Neighbouring Group Effects in Side Chain Reactions of Amino Acid Derivatives

by

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CONTENTS

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Last, but certainly not least, I am indebted to Lynne Wallace, for proof reading most of this thesis, for invaluable help in collating this thesis and for her continual support and friendship over the last year of my studies.

STATEMENT

This work contains no material which has been accepted for the award of any other degree or diploma in any other university or other tertiary institution, and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan or photocopying.

Martin Merrett (B.Sc. Hons.) January 10, 1997

PUBLICATIONS

Some of the work described in this thesis has been reported in the following publications:

"Stereoselective Synthesis of (2*S*,3*S*)-γ-Hydroxyvaline Utilising an Asymmetric Radical Hydrogen Bromide Addition", C. J. Easton, M. C. Merrett, *Tetrahedron*, **1996**, in press.

"Neighbouring Group Effects Promote Substitution Reactions over Elimination and Provide a Stereocontrolled Route to Chloramphenicol", *Tetrahedron*, **1996**, 52, 7025 (Appendix 1).

"Anchimeric Assistance in Hydrogen Atom Transfer Reactions on the Side Chains of Amino Acid Derivatives", C. J. Easton, M. C. Merrett, *J. Am. Chem. Soc.*, **1996**, 118, 3035 (Appendix 2).

"Crystal Structure of (*S*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloylvalinamide", $C_{17}H_{22}N_2O_4$, *Z. Krist.*, **1996**, 211, 289 (Appendix 3).

ABSTRACT

Ionic chlorination of a β,γ-dehydrovaline derivative has been shown to occur regiospecifically at the γ-allylic position, which has been attributed to neighbouring group participation by the protected carboxy group.

anti-Markovnikov hydrobromination of a β,γ-dehydrovaline derivative has been shown to occur stereoselectively, as a result of 1,2-asymmetric induction, to give diastereomers of a γ-functionalised valine derivative, which has been utilised in the stereocontrolled synthesis of a γ-hydroxyvaline diastereomer. This material was shown to be identical to the natural product, which was isolated from the plant species *Kalanchoe daigremontiana*.

1,4-Neighbouring group participation by a carboxy group has been discovered in hydrolysis reactions of *N*-phthaloyl β-bromophenylalanine, β-bromovaline and β-bromo-*p*-nitrophenylalanine derivatives using aqueous silver salts. The substitution process was enhanced when the carboxy group was protected as an amide rather than as an ester, which has been attributed to stabilisation of carbocation intermediates of reactions by the amido group, through a 1,4-interaction. The course of reactions of β-bromovaline and β-bromo-*p*-nitrophenylalanine derivatives is influenced by the neighbouring group effect of the protected carboxy group. Whereas elimination is the predominant reaction when the carboxy group is protected as an ester, substitution dominates when the carboxy group is protected as an amide. The effect of the neighbouring group to promote substitution over elimination has been exploited in the synthesis of a derivative of naturally occurring β-hydroxyvaline and a β-hydroxynitrophenylalanine derivative, which is a precursor to chloramphenicol.

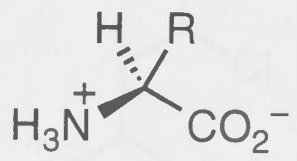
The first example of 1,4-neighbouring group participation and anchimeric assistance in radical reactions has been discovered. The rates of bromination of

derivatives of *N*-phthaloyl-protected phenylalanine, tyrosine and nitrophenylalanine are enhanced when the carboxy group is protected as an amide rather than as an ester, which has been attributed to 1,4-neighbouring group participation and stabilisation of electron deficient transition states by the amido group. The stereoselectivity of hydrogen abstraction determined through investigation of bromination reactions of derivatives of *N*-phthaloyl-protected deuterophenylalanine is greater when the carboxy group is protected as an amide than when protected as an ester, consistent with neighbouring group participation by the amido moiety. The deuterium isotope effect measured from reactions of amide derivatives of deuterophenylalanine was lower than that in reactions of corresponding ester derivatives, consistent with neighbouring group participation and stabilisation of the reaction transition state. Stabilisation of electron deficient transition states by the amido group in the radical bromination reactions of phenylalanine derivatives has been shown to occur through direct interaction with the developing charge at the β-position, through investigation of reactions of derivatives of *N*-phthaloyl-*p*-methylphenylalanine.

A derivative of *N*-bromophenylalaninamide has been shown to react *via* an apparent 1,4-hydrogen shift, but further investigation revealed that the mechanism of reaction involves intermolecular electron transfer to an amidyl radical intermediate followed by intramolecular deprotonation at the β-benzylic position of an intermediate aryl radical cation species by the amido moiety. The stereoselectivity of hydrogen abstraction determined by investigating reactions of deuterated analogues of an *N*-bromophenylalaninamide derivative was shown to be consistent with an intramolecular reaction. A methylphenylalanine derived *N*-bromoamide has been shown to react with high regioselectivity at the β-position, consistent with an intramolecular reaction.

INTRODUCTION

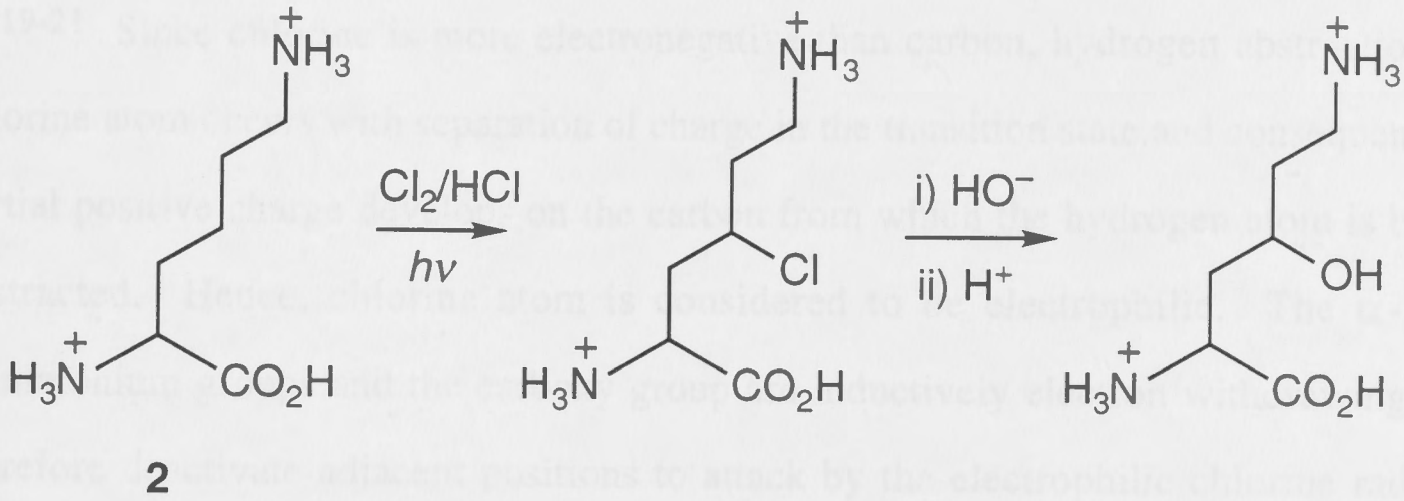
Amino acids occur in nature as the fundamental constituents of proteins, peptides and many other species.[1] To date, over five hundred naturally occurring amino acids have been reported, although only twenty occur commonly in proteins.[2-4] A particular class of amino acids, the mono-substituted α-amino acids **1**, possess a chiral α-carbon about which are arranged the amino and carboxy groups, the α-hydrogen and the side chain (R). It is the side chain which confers upon an amino acid its unique properties, which distinguish it physically, chemically and biologically.[1] Biosynthesis of many of the non-proteinogenic amino acids is presumed to occur through functionalisation of the side chains of proteinogenic amino acids.[5-7]



1

Amino acids have found importance as agrochemicals[8] and pharmaceuticals,[9] and in the food industry as flavours,[10] taste enhancers and sweeteners.[11] In addition, the use of analogues of natural amino acids has allowed a greater understanding of biochemical systems such as enzyme reaction mechanisms,[12,13] protein conformations[14-16] and regulatory interactions of peptides.[17] As a result of their widespread natural occurrence, physiological activity and potential applications in biological systems, intense interest has been focussed on the synthesis of α-amino acids.[18] α-Amino acids are sometimes unavailable from natural sources in quantities sufficient for thorough structural and biological testing and often it is only through the synthesis of these physiologically important compounds that it becomes possible to confirm both their structure and function.

Any synthesis of an α-amino acid should take into account the chirality at the α-carbon. One approach to the synthesis of unnatural amino acids involves the elaboration of proteinogenic α-amino acids through side chain modification. Complementary to the side chain modification of amino acids through the manipulation of pre-existing functionality is the regioselective free radical modification of proteinogenic amino acids. This latter approach is exemplified by the γ-chlorination and subsequent hydroxylation of lysine **2**, as described by Kollonitsch *et al.* (Scheme 1),[19-21] and has since been applied to the synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b** (Scheme 2)[22] and lactones of γ-hydroxy amino acids.[23]



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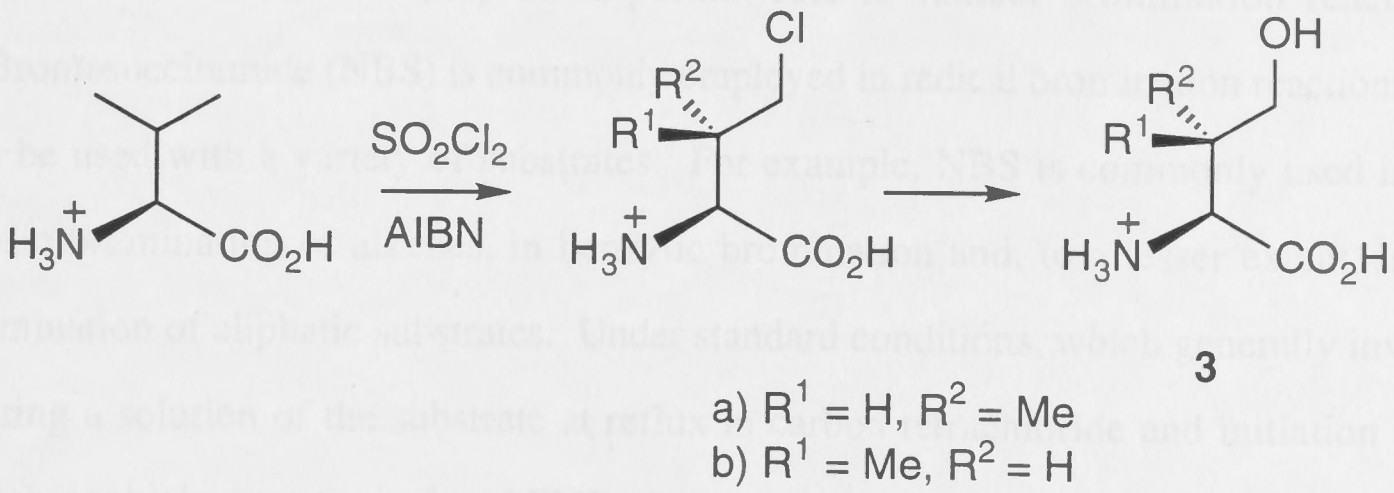
Scheme 1



3

a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H

Scheme 2

In halogenation reactions, regioselective hydrogen atom abstraction by halogen atom occurs as a result of several factors, which include product radical stability, steric effects and polar effects.[24] Radical stability is important when there is substantial carbon–hydrogen bond cleavage in the transition state, that is, a relatively late transition state, and consequently the transition state species exhibits significant radical character. By hindering the approach of the abstracting species or by constraint of the conformation of the product radical, steric factors can also affect the regioselectivity of reaction. Polar effects refer to the activating and deactivating effects resulting from charge development in the reaction transition state. For example, polar effects were used to explain the regioselectivity observed in the chlorination of lysine **2**, described above (Scheme 1).[19-21] Since chlorine is more electronegative than carbon, hydrogen abstraction by chlorine atom occurs with separation of charge in the transition state and consequently a partial positive charge develops on the carbon from which the hydrogen atom is being abstracted. Hence, chlorine atom is considered to be electrophilic. The α- and ε-ammonium groups and the carboxy group are inductively electron withdrawing and therefore deactivate adjacent positions to attack by the electrophilic chlorine radical. Consequently, reaction occurs at the γ-position, the position most distant from both the α- and ε-positions.

Polar effects also play an important role in radical bromination reactions. *N*-Bromosuccinimide (NBS) is commonly employed in radical bromination reactions and can be used with a variety of substrates. For example, NBS is commonly used in the allylic bromination of alkenes, in benzylic bromination and, to a lesser extent, in the bromination of aliphatic substrates. Under standard conditions, which generally involve heating a solution of the substrate at reflux in carbon tetrachloride and initiation from either azobisisobutyronitrile (AIBN) decomposition or ultra-violet irradiation, the electrophilic bromine atom is the chain-carrying species.[25] The most commonly accepted mechanism for reactions involving NBS is shown below (Scheme 3), in which the rate limiting step involves hydrogen abstraction by bromine atom from the substrate (RH).[26]

That is, the rate of reaction of a particular substrate reflects the ease with which hydrogen atom is abstracted from the substrate by bromine atom and hence reflects the rate of radical formation.

$$Br^{\bullet} + RH \rightarrow HBr + R^{\bullet}$$

$$HBr + NBS \rightarrow \text{succinimide} + Br_2$$

$$Br_2 + R^{\bullet} \rightarrow RBr + Br^{\bullet}$$

Scheme 3

Polar effects have been used to explain the relative rates of reactions of substituted toluenes with NBS (Table 1).[27,28] In these reactions a negative Hammett ρ value was obtained, which indicates that hydrogen abstraction occurs with development of partial positive charge on the carbon from which the hydrogen is abstracted (Figure 1). As seen in the reactions involving hydrogen abstraction by chlorine radical, the development of a partial positive charge is disfavoured by electron withdrawing substituents and hence the rate of reaction is diminished in the presence of these groups. For example, the rate of hydrogen atom abstraction from toluene was determined to be twenty times that for reaction of the electron deficient *p*-nitrotoluene.[27]

$$\underset{\delta-\bullet}{Br}\cdots\cdots\underset{}{H}\cdots\cdots\underset{\delta+\bullet}{CH_2\text{–}Ar}$$

Figure 1. Polar transition state in hydrogen abstraction by bromine atom.

substituent	k_{rel} (NBS)
p-OCH_3	11.7 ± 0.7
p-CH_3	2.56 ± 0.17
p-H (std)	1.00
p-Br	0.94 ± 0.03
p-NO_2	0.05

Table 1. Relative rates of reaction of substituted toluenes with NBS (per H) at 80 °C in carbon tetrachloride.[27]

In comparison with reactions involving hydrogen abstraction by chlorine atom, those involving hydrogen abstraction by bromine atom are affected to a greater extent by product radical stability. For reaction involving hydrogen abstraction by bromine atom, a later transition state with more product radical character is involved. Consequently, bromine atom is a much more selective hydrogen abstracting species than chlorine atom.[26]

Radical halogen abstraction reactions involving organotin reagents are also affected by product radical stability, steric effects and polar effects.[29] The mechanism of reactions involving organotin hydride reagents is shown in Scheme 4. The first irreversible step involving the organohalide is halogen abstraction by the stannyl radical ($R_3Sn^{\bullet}$), which is a chain-carrying species in the process. The rate constant for the chain propagating reaction of an organotin radical with a substrate (R'Br) is dependent on the nature of R'.[30-32] Consequently, in a competitive experiment involving the substrates R^1Br and R^2Br, the relative rates of reaction with an organotin hydride reagent reflect the ease with which halogen is transferred from each substrate to the stannyl radical ($R_3Sn^{\bullet}$), and hence reflect the relative rates of formation of the radicals $R^{1\bullet}$ and $R^{2\bullet}$.

$$R_3Sn^{\bullet} + R'Br \rightarrow R_3SnBr + R'^{\bullet}$$

$$R_3SnH + R'^{\bullet} \rightarrow R'H + R_3Sn^{\bullet}$$

Scheme 4

Polar effects have been used to explain the relative rates of reactions of series of substituted benzyl bromides, benzyl chlorides[33] and benzoyl chlorides[34] with tributyltin hydride, in which positive Hammett ρ values were obtained. The positive Hammett ρ values indicate that halogen abstraction is facilitated by electron withdrawing substituents and that the reactions proceed with the development of a partial negative charge on carbon from which halogen is abstracted (Figure 2). This is in direct contrast to the trend observed in reactions involving hydrogen abstraction by halogen atoms, which proceed with the development of a partial positive charge on carbon bearing the hydrogen, and can be rationalised by considering the relative electronegativity of tin and carbon. Carbon is more electronegative than tin and therefore partial positive charge develops on the tin while the development of negative charge occurs on carbon. Hence, stannyl radicals are considered nucleophilic.

$$\underset{\delta+\bullet}{n\text{-}Bu_3Sn}\cdots\cdots\cdots Br\cdots\cdots\cdots \underset{\delta-\bullet}{CH_2\text{–}Ar}$$

Figure 2. Polar transition state in bromine abstraction from benzyl bromides by tri-*n*-butyltin radical.

The application of radical reactions in the functionalisation and elaboration of amino acids is limited by the virtual insolubility of the amino acids in the solvents typically used in such processes. This problem can be overcome by suitable protection of the amino acids, however such protection has been shown to markedly affect the regioselectivity of radical reactions. For example, whereas hydrogen atom abstraction by bromine atom from *N*-acyl-α-amino acid derivatives generally favours formation of the corresponding α-carbon centred radicals (Figure 3),[35,36] formation of α-carbon centred radicals is disfavoured in the chlorination of free amino acids, such as lysine **2** (Scheme 1), due to the strong deactivating effect of the protonated amino group.

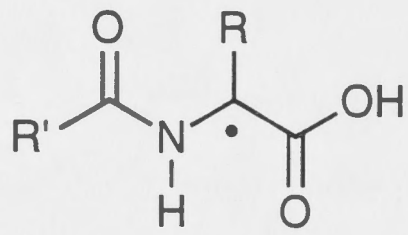
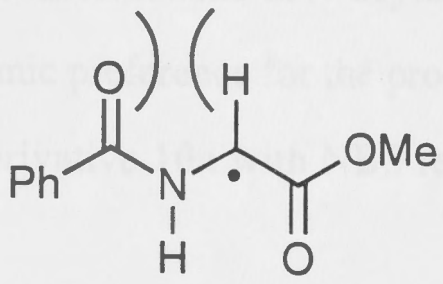


Figure 3. *N*-Acylamino acid α-centred radicals.

Stabilisation of an *N*-acylamino acid α-centred radical occurs from overlap of the semi-occupied *p*-orbital of the radical with the π-orbitals of the electron donating (dative) amido and electron withdrawing (capto) carboxy substituents. Radicals of this type are extremely stable and are referred to either as captodative,[37,38] merostabilised[39] or push-pull stabilised radicals.[40] The high stability of captodative radicals has been attributed to extended conjugation in the system. Extensive work in this area[41-50] has determined that the combined stabilisation provided by the substituents can be synergistic. As a result of the high stability and ease of formation of *N*-acylamino acid radicals, radical side chain functionalisation of *N*-acyl-protected α-amino acid derivatives is limited since α-centred

radical formation generally occurs in preference to side chain radical formation. This also destroys the chiral integrity at that position, leading to the formation of racemic products.

Maximum overlap of the semi-occupied *p*-orbital of the radical and the π-orbitals of the adjacent amido and carboxy substituents, and consequently maximum stability of the radical species, occurs when the *N*-acyl group and the carboxy group adopt a coplanar orientation. As the bulk of the side chain (R) increases, non-bonding interactions between this and the carboxy and amido groups also increase, resulting in the α-carbon centred radical adopting a non-planar orientation such that maximum orbital overlap, and hence maximum radical stability, cannot be attained. An illustration of the effect of these non-bonding interactions on the stability of captodative radicals is seen in the radicals **4** - **6** (Figure 4). By examining the relative rates of reactions of the amino acid derivatives **7a** - **9a** with NBS to give the corresponding bromides **7b** - **9b**, Easton and Hay[51]



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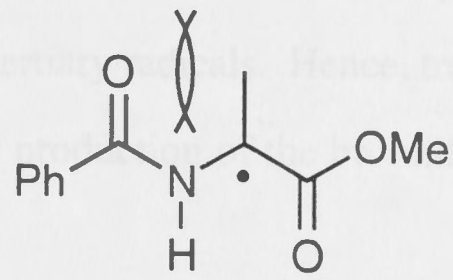

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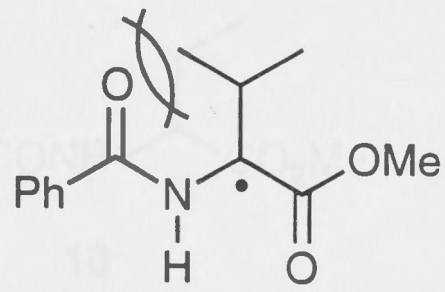
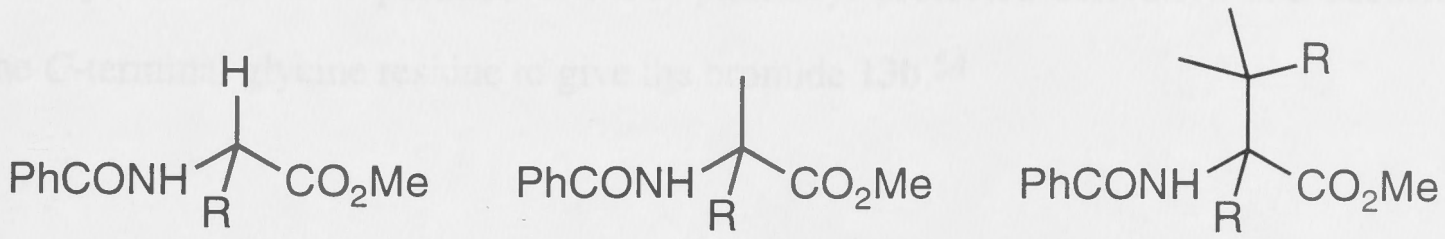


6

Figure 4. Non-bonding interactions associated with planar conformation of the radicals **4** - **6**.

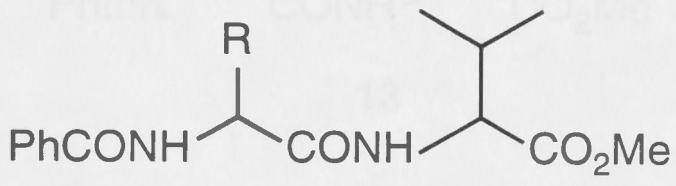
showed that the rate of formation of the secondary radical **4** was greater than that of the tertiary radical **5**, which in turn was greater than that of the tertiary radical **6**. The relative rates of formation of these species were attributed to their relative stability.



7 **8** **9**

a) R = H
b) R = Br

The destabilising influence of steric interactions between substituents associated with planar conformations of *N*-acylamino acid α-centred radicals outweighs the normal thermodynamic preference for the production of tertiary radicals. Hence, treatment of the dipeptide derivative **10a** with NBS results in the production of the bromide **10b** in high yield.[51,52]

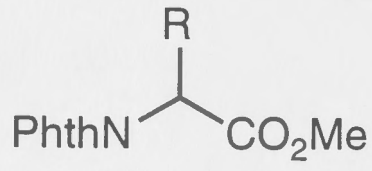


10

a) R = H
b) R = Br

In comparison with *N*-acylamino acid derivatives, *N*-phthaloyl-protected amino acid derivatives undergo hydrogen atom transfer from the α-position much less readily, due to the steric and electronic effects imposed by the phthaloyl group. For example,

reaction of *N*-phthaloylglycine methyl ester **11a** with NBS affords the bromide **11b** considerably less efficiently than the reaction of *N*-benzoylglycine methyl ester **7a** with NBS gives the bromide **7b**, as determined through competitive experiments.[53] Furthermore, whereas treatment of the *N*-benzoyl-protected dipeptide **12a** with NBS affords the derivative **12b** with incorporation of bromine onto the *N*-terminal glycyl moiety, bromine incorporation of the *N*-phthaloyl-protected derivative **13a** occurred at the *C*-terminal glycine residue to give the bromide **13b**.[54]



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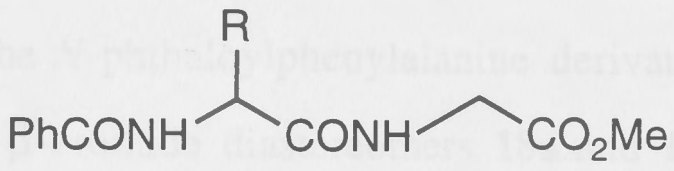
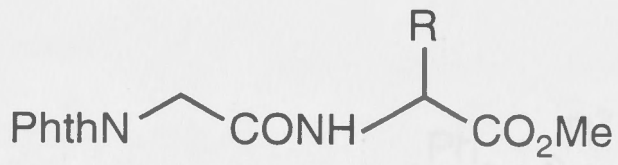
a) R = H
b) R = Br



12

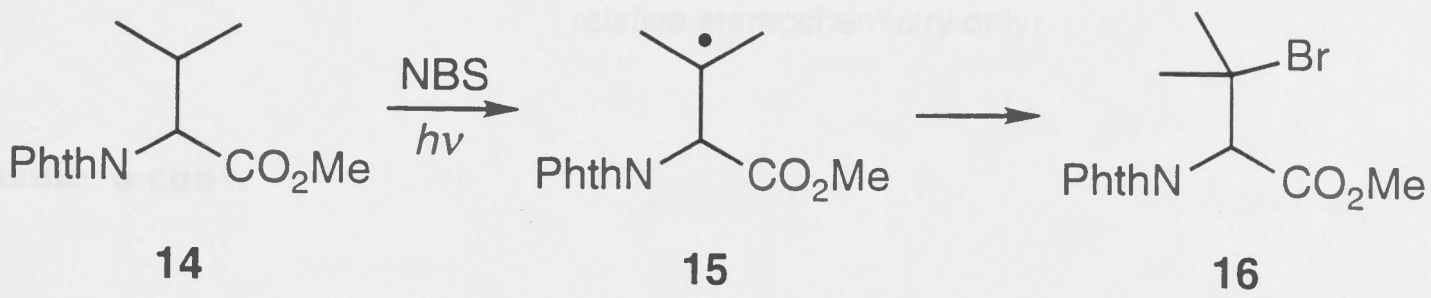
a) R = H
b) R = Br



13

Further investigation of the effect of the phthaloyl protecting group to limit α-carbon centred radical formation showed that abstraction of the α-hydrogen of *N*-phthaloylamino acid derivatives is disfavoured to the extent that reaction occurs regiospecifically on the side chains if suitably stabilised radicals can be formed.[51,54-57]

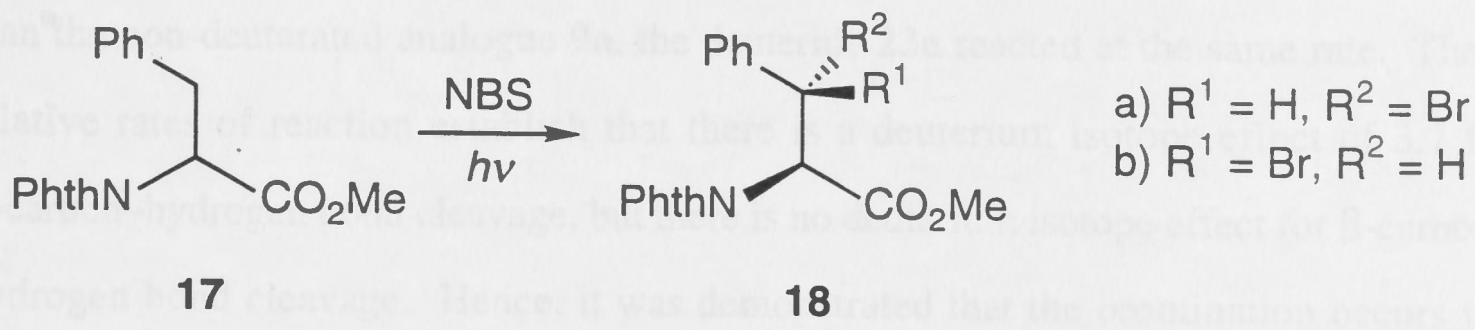
Whereas treatment of the *N*-benzoyl-protected valine derivative **9a** with NBS affords the dibromide **9b**, with initial formation of the α-centred radical **6**,[51,55-57] similar treatment of the *N*-phthaloylvaline derivative **14** with NBS affords the β-bromide **16** *via* the corresponding β-centred radical **15** (Scheme 5).[54]



14 **15** **16**

Scheme 5

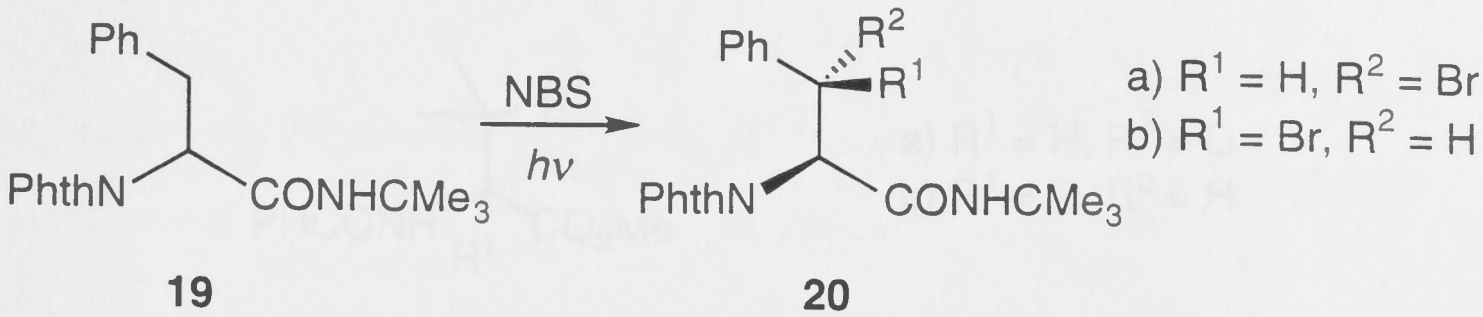
The *N*-phthaloylphenylalanine derivatives **17** and **19** showed similar regioselectivity of reaction to that of the valine derivative **14** when treated with NBS. Treatment of the *N*-phthaloylphenylalanine derivative **17** with NBS afforded a 1:1 mixture of the β-bromide diastereomers **18a** and **18b**, *via* the β-centred side chain radical **21**,[54] while the amide **19** reacted to give a 1:1 mixture of the bromides **20a** and **20b** (Scheme 6), *via* the radical **22**.[53]



17 **18**

(stereochemical descriptors show relative stereochemistry only)

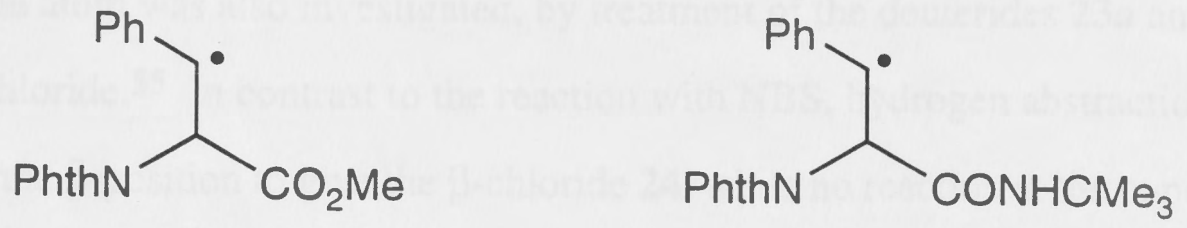
Scheme 6



19 **20**

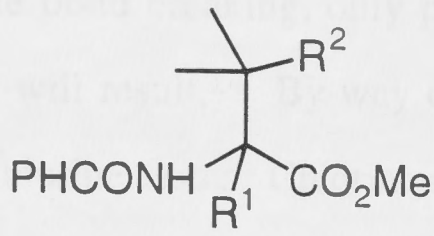
(stereochemical descriptors show relative stereochemistry only)

Scheme 6 cont.



21 **22**

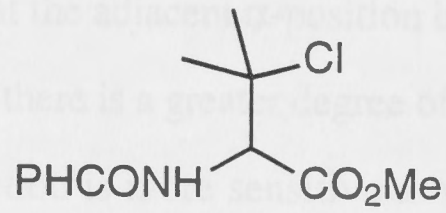
In the reaction of the valine derivative **9a** with NBS, the regioselectivity of hydrogen abstraction was determined through deuterium labelling experiments, by investigation of the relative rates of reactions of the deuterides **23a** and **23b** and the non-deuterated analogue **9a**.[51,55] Whereas the deuteride **23b** reacted 3.7 times slower than the non-deuterated analogue **9a**, the deuteride **23a** reacted at the same rate. These relative rates of reaction establish that there is a deuterium isotope effect of 3.7 for α-carbon–hydrogen bond cleavage, but there is no deuterium isotope effect for β-carbon–hydrogen bond cleavage. Hence, it was demonstrated that the bromination occurs *via* hydrogen atom abstraction from the α-position of the valine derivative **9a** and yields the dibromide **9b**, the final product of the reaction with NBS.



23

a) $R^1 = H, R^2 = D$
b) $R^1 = D, R^2 = H$

In addition to determining the regioselectivity of hydrogen abstraction from reaction of the valine derivative **9a** with NBS, the regioselectivity of hydrogen abstraction by chlorine atom was also investigated, by treatment of the deuterides **23a** and **23b** with sulfuryl chloride.[55] In contrast to the reaction with NBS, hydrogen abstraction occurred mainly at the β-position to give the β-chloride **24**, while no reaction at the α-position was observed. A deuterium isotope effect of 1.3 for abstraction of the β-hydrogen was obtained in the reaction of the deuteride **23a**.



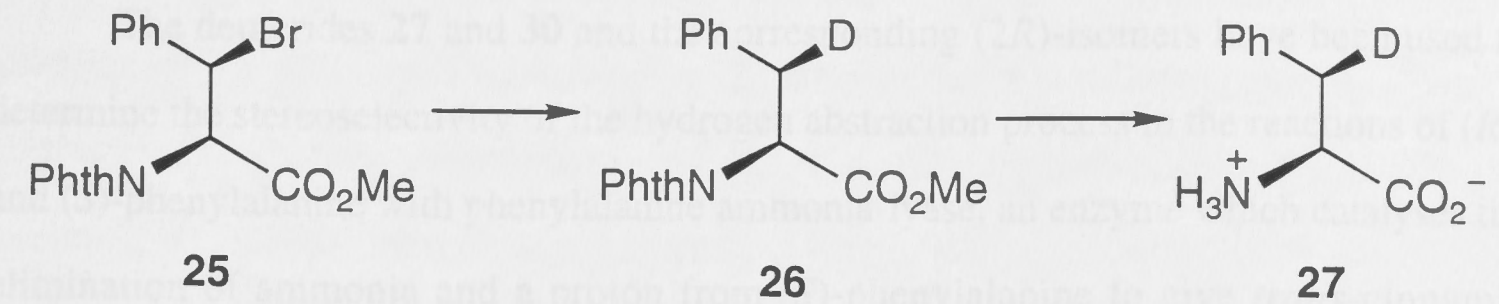
24

Deuterium isotope effects[24] arise due to the difference of nearly 6.3 kJ/mole between the zero-point energies of carbon-hydrogen and carbon-deuterium bonds, because of the effect of the larger mass of deuterium compared to hydrogen on stretching and bending frequencies. A portion of the energy associated with these stretching and bending frequencies can be lost in transition states during which these bonds are ruptured. In a symmetrical transition state, that is one in which there is an equal amount of bond breaking and bond making, most of this energy is lost and a large deuterium

isotope effect will arise. If the transition state is not symmetrical, for example, if it possesses little bond breaking, only part of this energy is lost and a greatly reduced isotope effect will result.[24] By way of illustration, consider hydrogen abstraction by bromine and chlorine atoms. Chlorine atom is a more reactive radical than bromine atom and hydrogen abstraction by the former involves an earlier transition state with less bond breaking, such that a lower deuterium isotope effect results.[24]

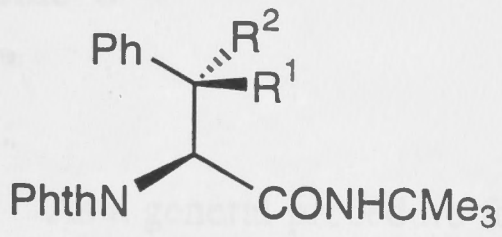
The contrast in selectivity observed in the reactions of the *N*-benzoylvaline derivative **9a** involving hydrogen abstraction by chlorine and bromine atom[55] was interpreted in terms of the relative degrees of carbon–hydrogen bond homolysis in their transition states. The greater deuterium isotope effect of 3.7 for α-carbon–hydrogen bond cleavage in the reaction with NBS compared to the effect of 1.3 for β-carbon–hydrogen bond homolysis in the chlorination reaction indicates a greater degree of bond homolysis in the transition state in the former case. With little development of radical character in the transition state of the chlorination reaction, the regioselectivity in this case is controlled by the inductive electron-withdrawing effect of the amido and carboxy groups acting to retard attack at the adjacent α-position by the electrophilic chlorine atom. In the reaction involving NBS there is a greater degree of radical character in the transition state. Consequently, the reaction is more sensitive to radical stability and α-hydrogen abstraction occurs to give the captodative α-centred radical **6**.

Brominated *N*-phthaloylamino acid derivatives have been used in the syntheses of a variety of side chain functionalised amino acid derivatives. For example, the stereoisomers **27** and **30** of [3-$^2H_1$]-phenylalanine have been prepared,[58] by treatment of the (*S*)-phenylalanine derived bromides **25** and **28** with deuterium gas over 5% palladium-on-carbon and hydrolysis of the resultant deuterides **26** and **29**, respectively (Scheme 7).



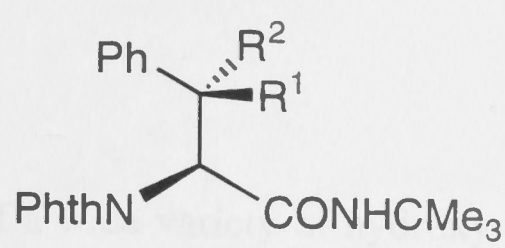
Scheme 7

Under identical conditions to those described above, the deuterated phenylalaninamides **31a** and **31b** have also been prepared with retention of configuration at the β-position from the (*S*)-phenylalanine derived bromides **32a** and **32b**, respectively, by treatment with deuterium over 5% palladium-on-carbon.[59]



31

a) R^1 = H, R^2 = D
b) R^1 = D, R^2 = H

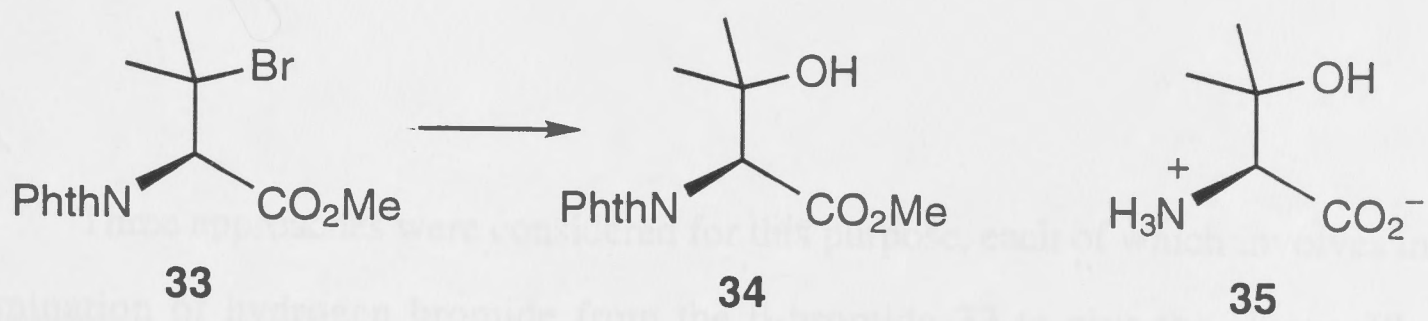


32

a) R^1 = H, R^2 = Br
b) R^1 = Br, R^2 = H

The deuterides **27** and **30** and the corresponding (2*R*)-isomers have been used to determine the stereoselectivity of the hydrogen abstraction process in the reactions of (*R*)- and (*S*)-phenylalanine with phenylalanine ammonia-lyase, an enzyme which catalyses the elimination of ammonia and a proton from (*S*)-phenylalanine to give *trans*-cinnamic acid.[58]

Brominated amino acid derivatives have also been utilised in syntheses of an important class of amino acids, the hydroxy amino acids. For example, the β-bromovaline derivative **33** derived from (*S*)-valine has been converted to the alcohol **34**, a derivative of naturally occurring (*S*)-β-hydroxyvaline **35**.[60]

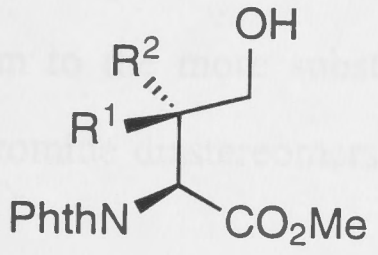


33 **34** **35**

Scheme 8

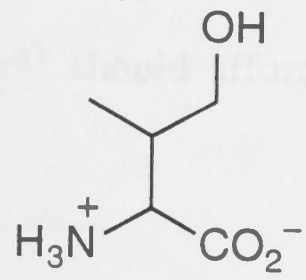
As a general procedure for the preparation of a wide variety of hydroxy amino acids this method is limited, however, since the introduction of the functional group occurs at the site of the most stable side chain radical, the position of which is determined in the radical bromination reaction of the *N*-phthaloylamino acid derivative. Thus, whereas the β-hydroxyvaline derivative **34** can be prepared from the corresponding β-bromide **33**, the derivatives **36a** and **36b** of the γ-hydroxyvaline isomers **3a** and **3b** cannot be obtained directly using this approach, since formation of an unstable primary

radical would be required in the latter case. Therefore, an aim of the present work was to manipulate the regiospecifically functionalised bromide **33** in order to achieve relocation of the bromine functionality to the γ-position, a position removed from the site at which the most stable side chain radical is formed in the radical bromination with NBS, and to utilise this in the synthesis of naturally occurring γ-hydroxyvaline **37**, of which the stereochemistry is unknown.



36

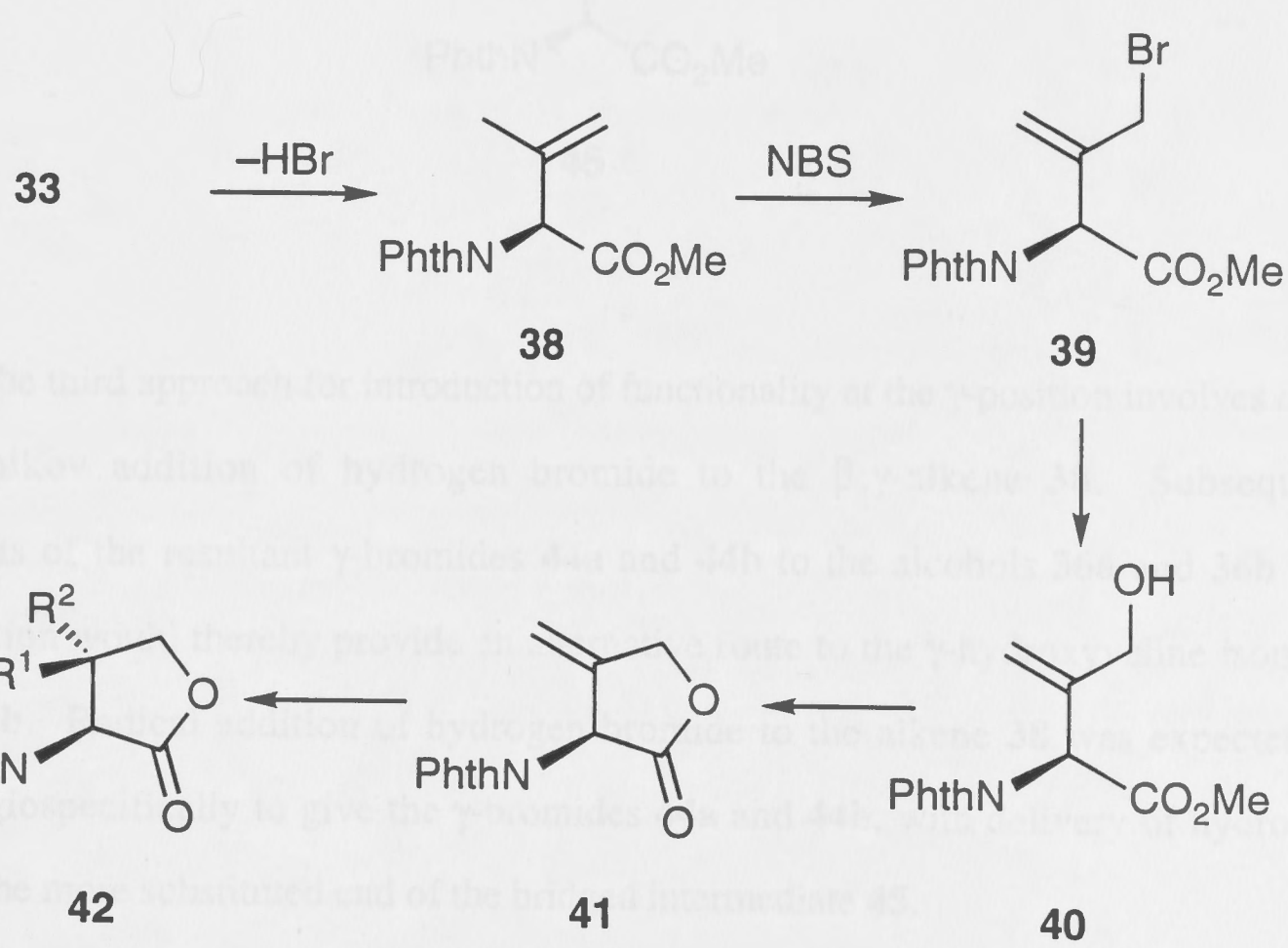
a) $R^1 = H$, $R^2 = Me$
b) $R^1 = Me$, $R^2 = H$



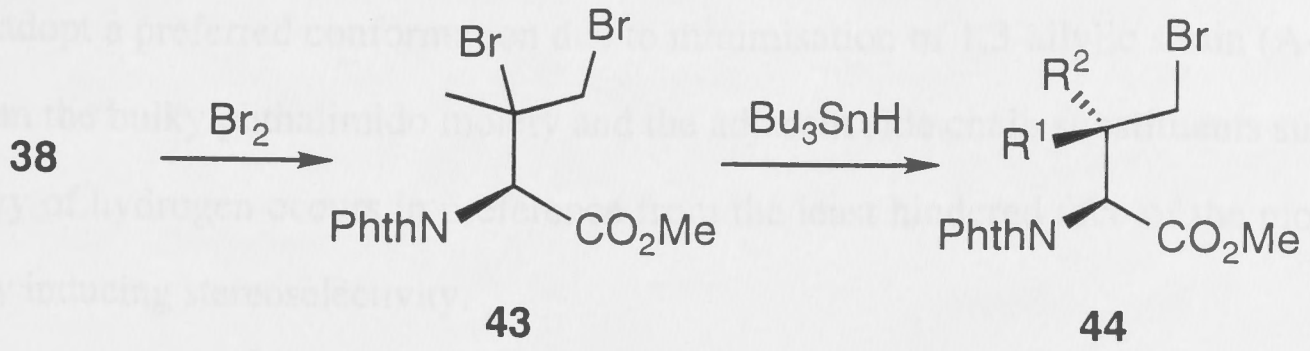
37

Three approaches were considered for this purpose, each of which involves initial elimination of hydrogen bromide from the β-bromide **33** to give the alkene **38**, and subsequent elaboration to introduce functionality at the γ-position. In the first approach, it was thought that introduction of functionality at the γ-position could be achieved through allylic bromination of the alkene **38** to give the bromide **39**. Following hydrolysis to the alcohol **40** and lactonisation, it was anticipated that hydrogenation would afford the lactone **42** (Scheme 9), from which the γ-hydroxyvaline diastereomers **3a** and **3b** could be obtained by hydrolysis. In addition to providing a route to γ-hydroxyvaline **37**, the process is of further interest due to the possibility of stereoselectivity in the hydrogenolysis of the exocyclic double bond of the lactone **41**. Therefore, the process could provide a stereocontrolled route to γ-hydroxyvaline **37**.

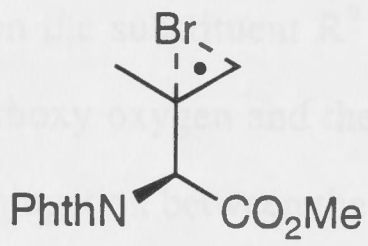
The second approach considered for the synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b** involves addition of molecular bromine to the alkene **38** and regioselective reduction at the tertiary position of the resultant dibromide **43** to give the γ-bromide isomers **44a** and **44b** (Scheme 10). Through hydrolysis of the γ-bromides **44a** and **44b** to the γ-alcohols **36a** and **36b** and deprotection, it was anticipated that the free amino acid diastereomers **3a** and **3b** could be obtained. Regioselective reduction of the dibromide **43** at the tertiary position using tri-*n*-butyltin hydride was expected. Following removal of a bromine to give the bridged radical **45**, delivery of hydrogen atom to the more substituted end of the bridged intermediate[61] should afford the γ-bromide diastereomers **44a** and **44b**.



Scheme 9



Scheme 10



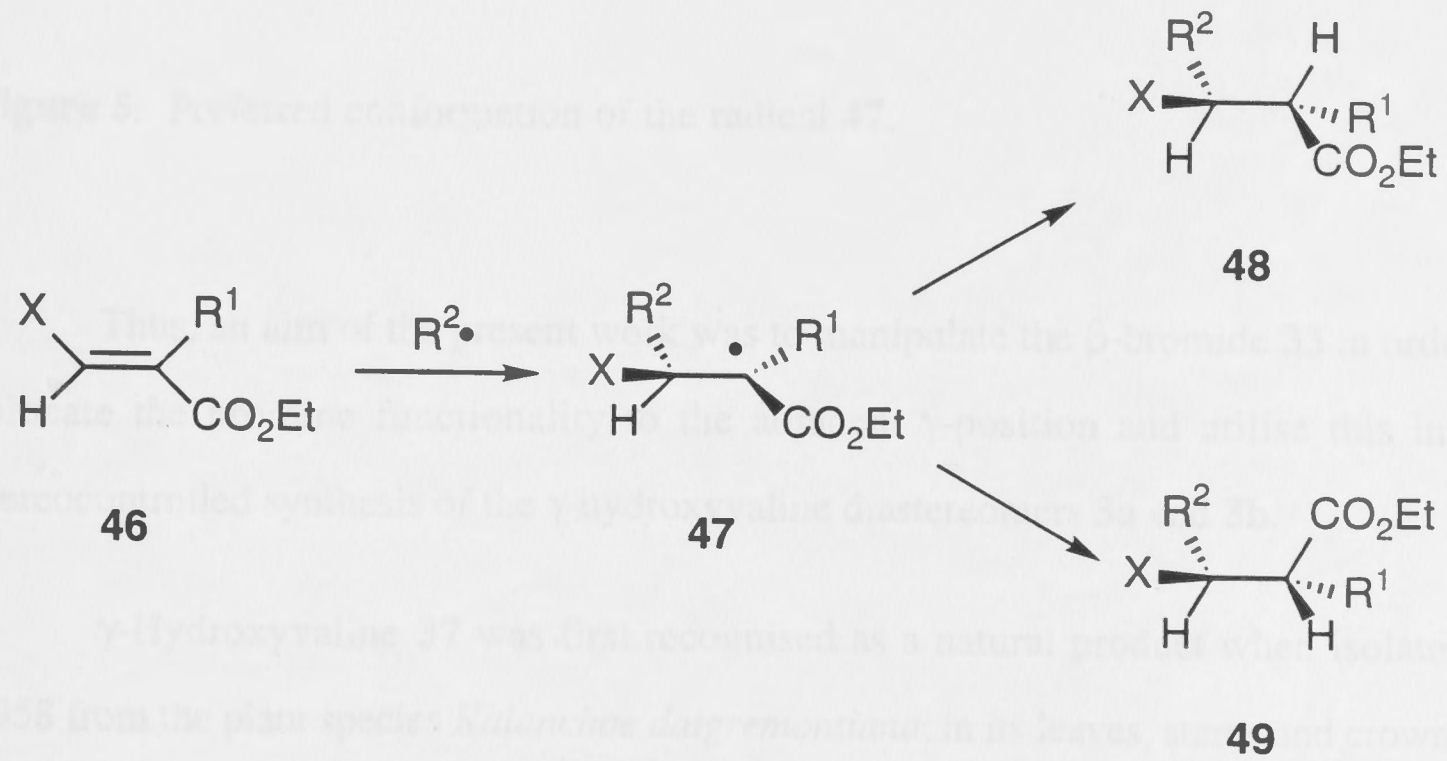
45

The third approach for introduction of functionality at the γ-position involves *anti*-Markovnikov addition of hydrogen bromide to the β,γ-alkene **38**. Subsequent hydrolysis of the resultant γ-bromides **44a** and **44b** to the alcohols **36a** and **36b** and deprotection would thereby provide an alternative route to the γ-hydroxyvaline isomers **3a** and **3b**. Radical addition of hydrogen bromide to the alkene **38** was expected to occur regiospecifically to give the γ-bromides **44a** and **44b**, with delivery of hydrogen atom to the more substituted end of the bridged intermediate **45**.

It was thought that both reduction of the dibromide **43** and addition of hydrogen bromide to the alkene **38** would proceed *via* the intermediate radical **45** to give the γ-bromides **44a** and **44b**. While it was envisaged that these reactions could be used to introduce bromine functionality at the γ-position, the reactions are of further interest due

to the possibility of stereoselectivity, through 1,2-asymmetric induction. The radical **45** could adopt a preferred conformation due to minimisation of 1,3-allylic strain (A-strain) between the bulky phthalimido moiety and the adjacent side chain substituents such that delivery of hydrogen occurs in preference from the least hindered face of the molecule, thereby inducing stereoselectivity.

There have been many reports of 1,2-stereoinduction in radical reactions.[62-81] The stereochemical outcome in these reactions is influenced by several factors, which include minimisation of 1,3-allylic strain,[64-76] electronic effects[69,77-80] and intramolecular hydrogen bonding.[81] For example, the radical **47**, produced from radical addition to the alkene **46**, underwent hydrogen addition to give the adduct **48** in preference to the isomer **49** when the substituent R^2 was larger than X, as a result of minimised strain between the carboxy oxygen and the substituents on the chiral centre (Scheme 11).[65] As a result of conjugation between the radical centre and the ester group



46 **47** **48** **49**

Scheme 11

of the radical **47**, the three carbons of the chiral centre, the radical centre and the carboxy group and the two oxygens of the ester lie almost in one plane. Allylic strain is smallest if the radical adopts a preferred conformation in which the carbon–hydrogen bond of the chiral centre points in the direction of the carbonyl oxygen (Figure 5). In this preferred conformation, the substituent X shields one face of the adjacent radical, while the substituent R^2 blocks the other. The bulk of these substituents controls the direction of attack.[65] Hence, and by analogy, reduction of the dibromide **43** with tri-*n*-butyltin hydride and radical addition of hydrogen bromide to the alkene **38** have the potential to occur stereoselectively as a result of 1,2-stereoinduction.

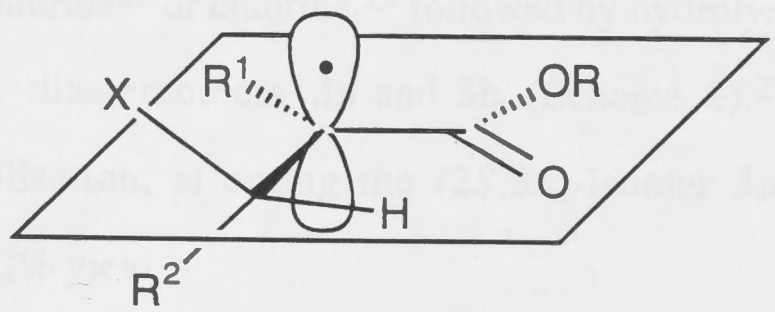


Figure 5. Preferred conformation of the radical **47**.

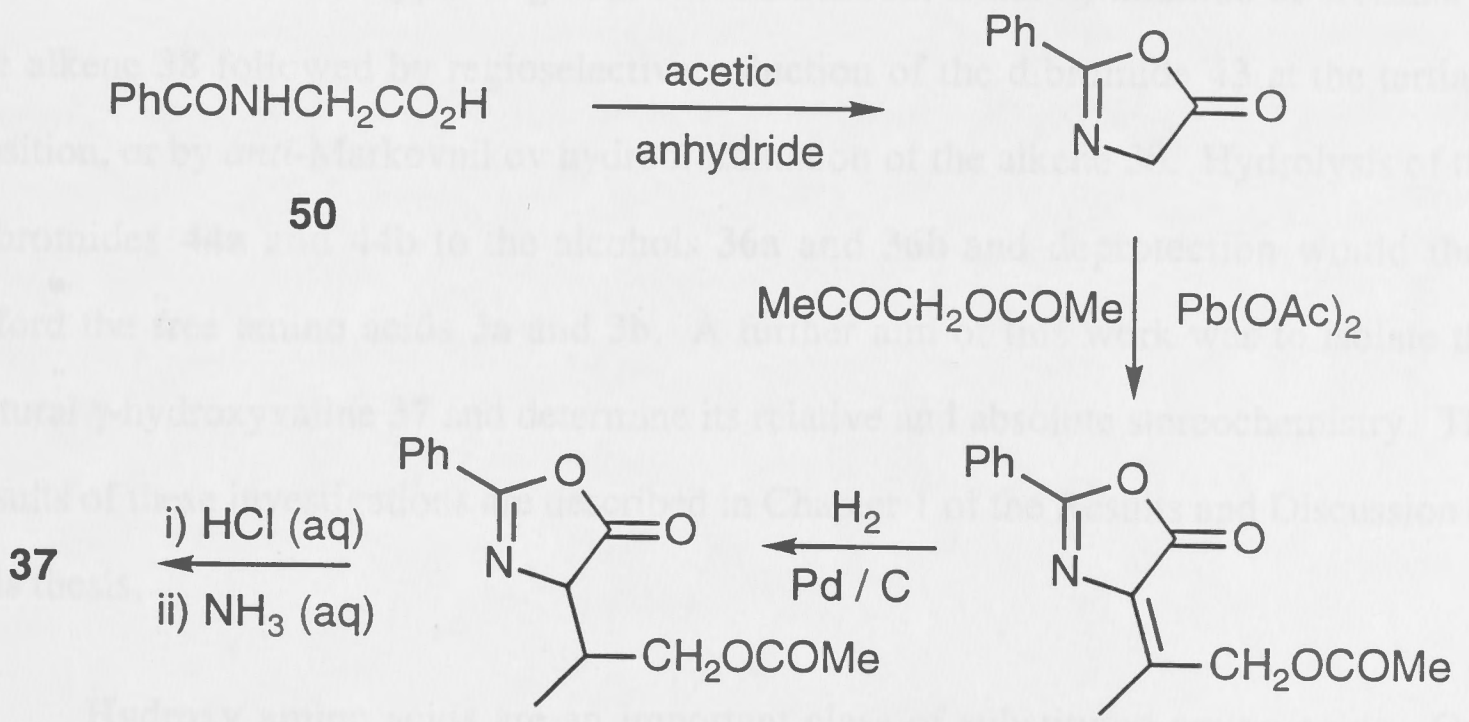
Thus, an aim of the present work was to manipulate the β-bromide **33** in order to relocate the bromine functionality to the adjacent γ-position and utilise this in the stereocontrolled synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b**.

γ-Hydroxyvaline **37** was first recognised as a natural product when isolated in 1958 from the plant species *Kalanchoe daigremontiana*, in its leaves, stems and crowngall tumours.[82] The relative stereochemistry of the natural product **37** has yet to be reported. Therefore, another aim of the present work was to isolate the natural product and determine its relative and absolute stereochemistry. Subsequent to its isolation in 1958,

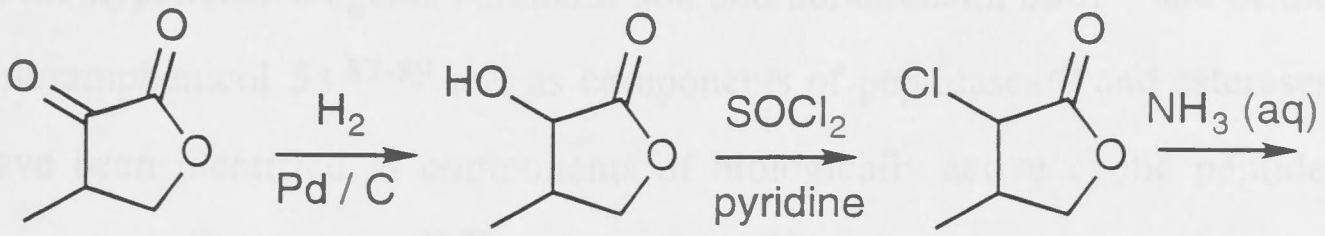
γ-hydroxyvaline **37** was obtained as a degradation product of cephalosporin C,[83] and has since been utilised to establish the infidelity of the proof-reading mechanism of the amino-acylation of tRNA by valyl-tRNA synthetases from *Saccharomyces cerevisiae* and *Escherichia coli*.[84]

Few syntheses of γ-hydroxyvaline **37** have been described. A four step procedure beginning from hippuric acid **50** has been reported, however, the procedure required the separation of diastereomers and gave the racemic product **37** (Scheme 12).[85] An alternative synthesis from α-keto-β-methyl-γ-butyrolactone **51** was neither diastereoselective nor enantioselective (Scheme 13).[82]

Another approach involved free radical chlorination of (*S*)-valine, by treatment with either sulfuryl chloride[22] or chlorine,[23] followed by hydrolysis to give a mixture of the γ-hydroxyvaline diastereomers **3a** and **3b** (Scheme 2).[22] The isomers were separated by crystallisation, affording the (2*S*,3*S*)-isomer **3a** in 6% yield and the diastereomer **3b** in 0.2% yield.



Scheme 12



51

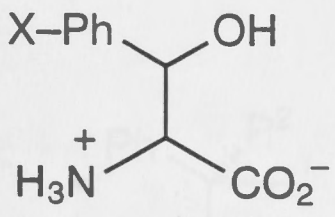
Scheme 13

In summary, three approaches towards the stereocontrolled synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b** investigated in the present work each involved elimination of hydrogen bromide from the β-bromide **33** to give the alkene **38**. One procedure involved allylic bromination of the alkene **38** and conversion to the lactone **41**, with subsequent asymmetric hydrogenation and deprotection to give the amino acids **3a** and **3b**. In addition, it was anticipated that the γ-bromides **44a** and **44b** could be obtained stereoselectively, through 1,2-stereoinduction, either by addition of bromine to the alkene **38** followed by regioselective reduction of the dibromide **43** at the tertiary position, or by *anti*-Markovnikov hydrobromination of the alkene **38**. Hydrolysis of the γ-bromides **44a** and **44b** to the alcohols **36a** and **36b** and deprotection would then afford the free amino acids **3a** and **3b**. A further aim of this work was to isolate the natural γ-hydroxyvaline **37** and determine its relative and absolute stereochemistry. The results of these investigations are described in Chapter 1 of the Results and Discussion of this thesis.

Hydroxy amino acids are an important class of substituted amino acids. One particular type of hydroxy amino acids of interest are β-hydroxy amino acids, which are widespread in nature and play essential physiological roles. Examples of naturally occurring β-hydroxy amino acids include serine and threonine. β-Hydroxyphenylalanine

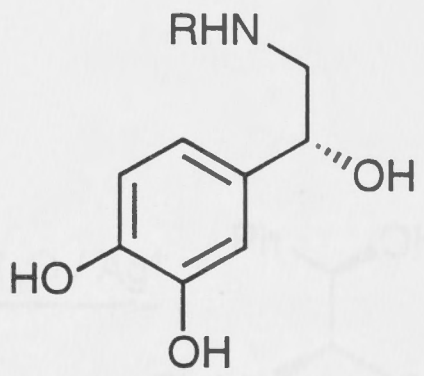
52a and β-hydroxytyrosine **52b** have been implicated as precursors in the biosynthesis of the hypertensive agents adrenalin **53a** and noradrenalin **53b**,[86] and of the antibiotic chloramphenicol **54**,[87-89] and as components of peptidases[90] and esterases.[5-7] They have been identified as components of biologically active cyclic peptides, such as vancomycin,[91] lysobactin[92,93] and bouvardin,[94] and are themselves of interest as enzyme inhibitors.[95]

The conversion of brominated *N*-phthaloylamino acid derivatives into hydroxy amino acids and their derivatives has been investigated previously.[60,96] Treatment of the bromoester **25** with aqueous silver nitrate in acetone afforded a 2:1 mixture of the alcohols **55** and **56**, while the isomer **28** reacted to give the alcohol **55**. Consistent with these results, a 1:1 mixture of the bromophenylalanine derivatives **25** and **28** afforded the corresponding alcohols **55** and **56** in the ratio 5:1 (Scheme 14).[60]



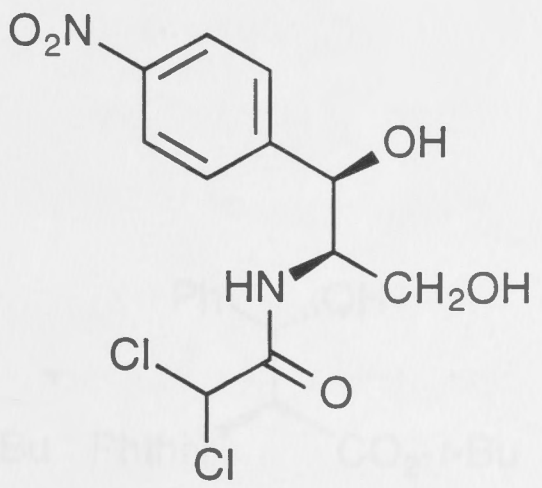
52

a) X = *p*-H
b) X = *p*-OH

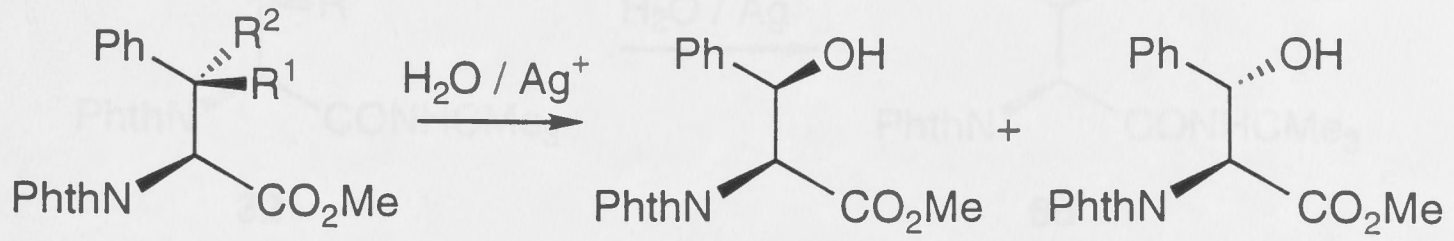


53

a) R = Me
b) R = H



54

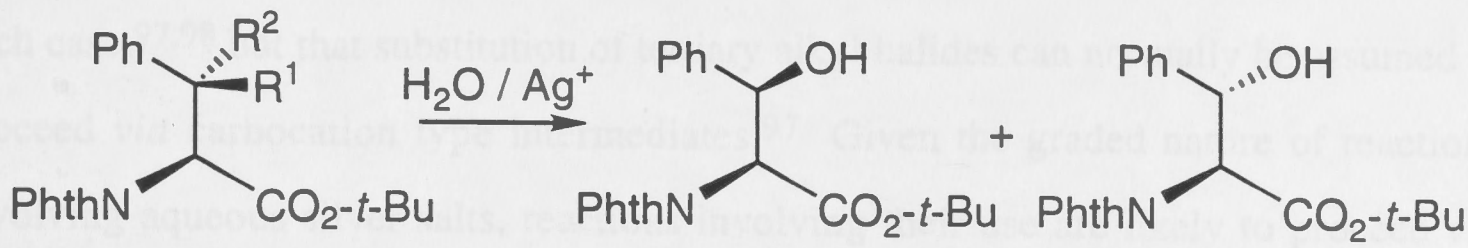


55 **56**

25) R^1 = Br, R^2 = H
28) R^1 = H, R^2 = Br

Scheme 14

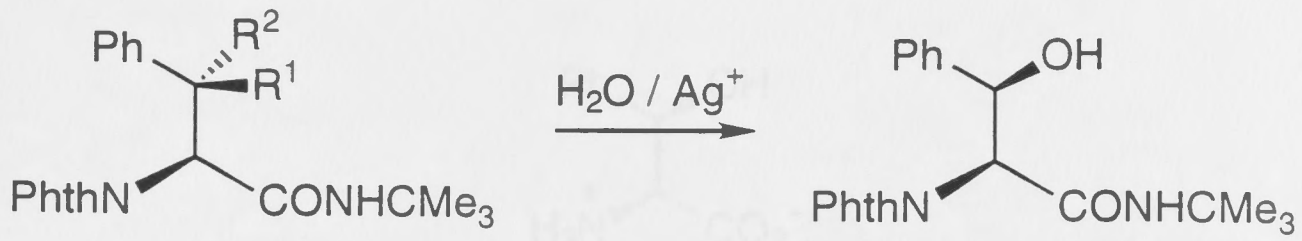
Similar treatment of a 1:1 mixture of the bromides **57a** and **57b** with aqueous silver nitrate afforded the alcohols **58** and **59** in the ratio 8:1 (Scheme 15), while a 1:1 mixture of the bromides **32a** and **32b** reacted to give solely the alcohol **60** (>99.9% d.e.) (Scheme 16).[96]



57 **58** **59**

a) R^1 = H, R^2 = Br
b) R^1 = Br, R^2 = H

Scheme 15



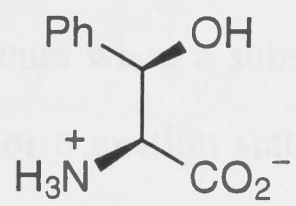
32 **60**

a) R^1 = H, R^2 = Br
b) R^1 = Br, R^2 = H

Scheme 16

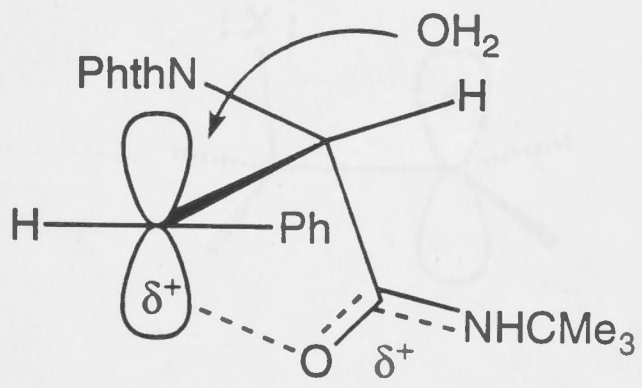
Silver salts were employed for the transformations of the brominated amino acid derivatives **25**, **28**, **32a**, **32b**, **57a**, and **57b** to the corresponding alcohols **55**, **56**, **58**, **59** and **60**, since mild, non-basic conditions were required due to the possibility of racemisation at the α-centre and elimination of hydrogen bromide, and also to avoid undesirable reactions of the phthalimido group due to its base-sensitivity. Using these conditions, no racemisation or unwanted side-reactions occurred. Silver ion induced reactions of organohalides have been shown to occur with graded S_N1-S_N2 character, the varying degree of which is dependent on the solvent, silver salt and bromide structure in each case,[97,98] but that substitution of tertiary alkyl halides can normally be assumed to proceed *via* carbocation type intermediates.[97] Given the graded nature of reactions involving aqueous silver salts, reactions involving their use are likely to proceed *via* electron deficient intermediates.

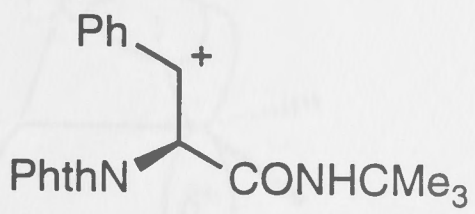
Subsequent deprotection of both the ester **55**[60,96] and the amide **60**[96] through acid catalysed hydrolysis afforded the free amino acid **61**. Hence, reactions involving hydrolysis of brominated *N*-phthaloylamino acid derivatives to give corresponding hydroxylated amino acid derivatives have the potential to be used in syntheses of a variety of hydroxy amino acids.



61

The dramatic increase in the stereoselectivity of reaction of the bromoamides **32a** and **32b** compared to the bromoesters **25** and **28**, and **57a** and **57b**, was attributed to neighbouring group participation by the amido substituent.[96] The bromoamide **32b** reacts with complete retention of configuration to give the alcohol **60**, while the bromoamide **32a** reacts with inversion of stereochemistry to give the same. Hence, it was postulated that the high stereoselectivity of reaction of the bromoamide **32b** was due to greater stabilisation of the carbocation intermediate **62** by the amido group (Figure 6), than by the ester group in the reactions of the esters **25** and **28**, and **57a** and **57b**. As a consequence of this stabilisation, the conformation of the carbocation was presumed to be locked, such that nucleophilic attack by water could only occur from the face opposite the amido group to give the alcohol **60**.[96]





62

Figure 6. Stabilisation of the carbocation **62** by the amido group.

Neighbouring group participation is a term which encompasses all reactions which involve non-electrostatic, through-space interactions between groups within the same molecule.[99] This phenomenon occurs when a substituent within a molecule interacts with, or stabilises an intermediate or transition state by becoming bonded or partially bonded to the reaction centre.[100] If the transition state of a rate-determining step is stabilised in this way, an increased reaction rate results and the neighbouring group participation is then said to provide anchimeric assistance.[100] Reactions involving neighbouring group participation can be classified as 1,x-, where x is the number of ring atoms in the cyclic transition state structure. For example, for 1,4-neighbouring group participation, such as that shown in Figure 6, a 4-membered cyclic transition state structure is formed.

Many examples of neighbouring group participation involving a wide variety of functional groups have been described previously.[99,100] One of the most commonly encountered forms of neighbouring group participation occurs in halogen addition to alkenes. The intermediate cation contains an electron-deficient carbonium ion carbon and a halogen with non-bonding electron pairs.[101] Consequently, there is a tendency for overlap to produce a cyclic halonium ion (Figure 7). The existence of halonium ion species is evident from the *trans*-addition of halogens to alkenes.

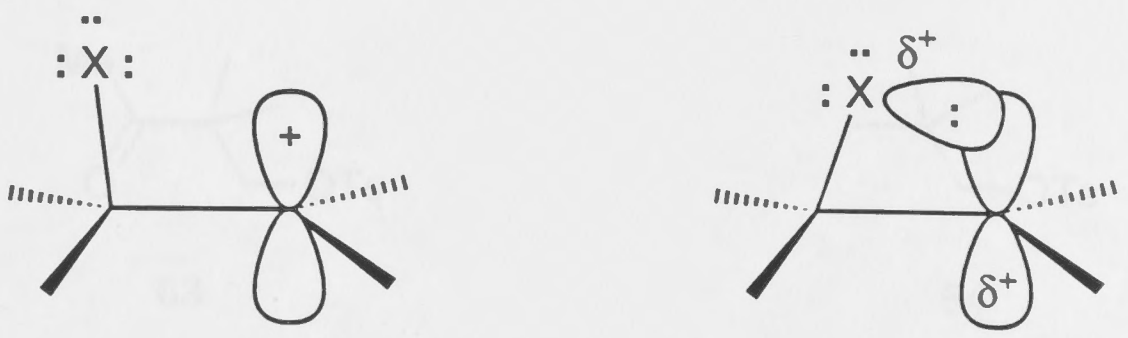
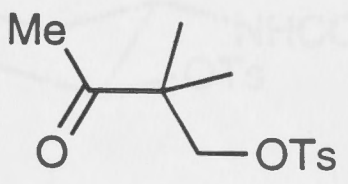


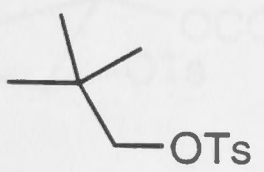
Figure 7. Formation of a cyclic halonium ion.

The extent of interaction and neighbouring group participation by the halogen with the adjacent carbonium ion, and hence the symmetrical nature of the halonium ion intermediate decreases in the order I > Br > Cl, which is consistent with the known ease with which these elements increase their valency.[100,102] Consequently, the bridged nature of iodonium and bromonium ions is greater than that of chloronium ions, such that the carbonium ion character of the chloronium ion is much greater than that of the corresponding bromonium and iodonium ions.[103] Halonium ions have been proposed as intermediates in halolactonisation reactions of γ,δ-unsaturated carboxylic acids and ester derivatives.[104]

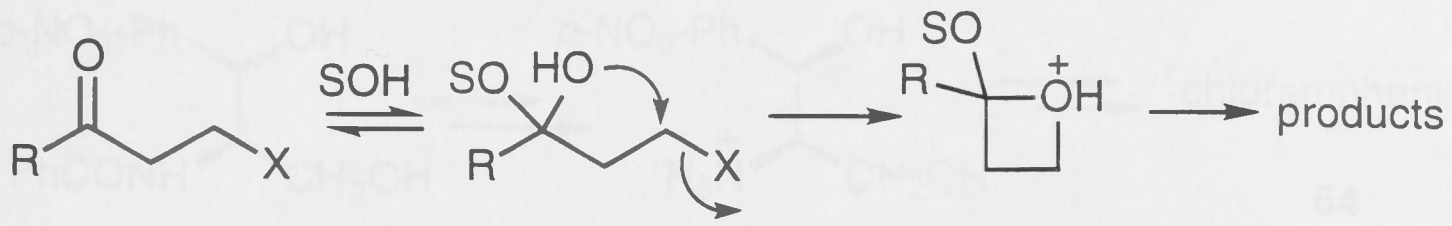
Carbonyl compounds such as ketones and aldehydes can be involved in neighbouring group participation,[100] including the rare 1,4-participation. Solvolysis of the ketone **63** in trifluoroacetic acid occurs *ca.* 10^7 times faster than the substitution of neopentyl tosylate **64**, which was attributed to direct participation by the carbonyl group.[105,106] In some cases, participation by a carbonyl group occurs through reaction of an adduct of the nucleophile and the carbonyl compound, such as an acetal,[106-108] and not the carbonyl group itself (Scheme 17).



63



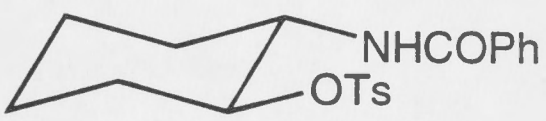
64



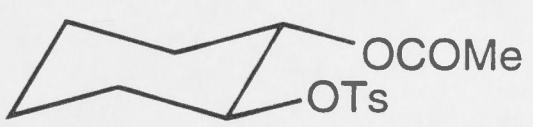
(where SOH = MeOH, for example)

Scheme 17

Ester and amide groups can also be involved in neighbouring group participation.[100,109-112] The extent of neighbouring group participation and anchimeric assistance displayed by amides is known to be larger than that shown by esters. For example, Winstein *et al.*[113] showed that the solvolysis of *trans*-2-benzamidocyclohexyl tosylate **65** in absolute ethanol proceeds 200 times faster than reaction of the corresponding *trans*-2-acetoxycyclohexyl tosylate **66** where neighbouring group participation had already been demonstrated.[114] Consistent with this proposal, the oxygen of an amide is approximately 10^6 times more basic than the oxygen of an ester.[115]

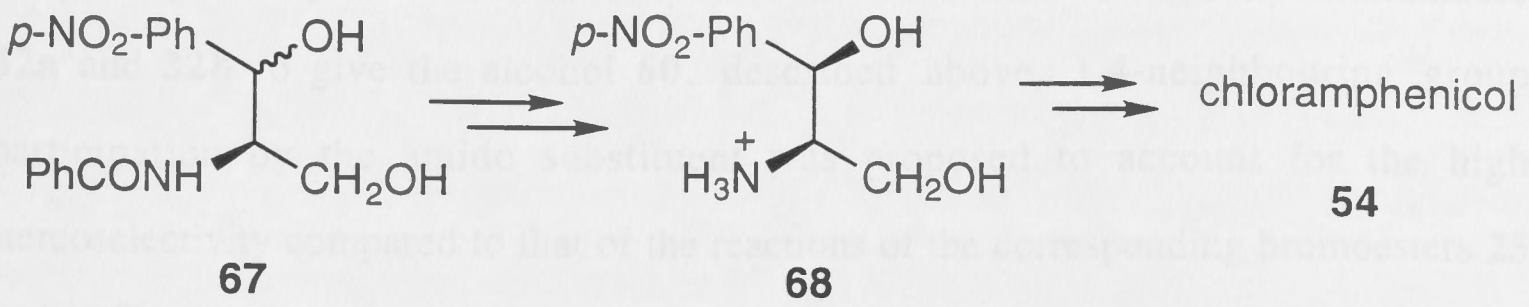


65



66

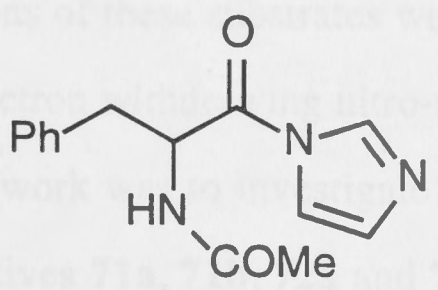
1,5-Neighbouring group participation by a benzamido group has been demonstrated in the hydrolytic rearrangement of the diastereomeric benzamides **67**, which was utilised in the stereocontrolled synthesis of chloramphenicol (Scheme 18).[116]



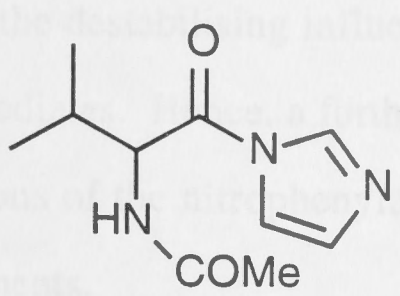
67 **68** **54**

Scheme 18

The chemical and biochemical implications of amide participation in reactions of amino acid derivatives have attracted considerable attention.[113,116-123] For example, it appears that the biochemistry of asparagine incorporated in peptides is influenced by the interaction of the side chain aminocarbonyl moiety with the peptide bonds,[117-121] while amides derived from either the amino[116,122] or carboxy group[123] of an amino acid are known to be able to act as nucleophiles or provide anchimeric assistance in solvolysis reactions, mainly *via* 1,5-participation. Neighbouring group participation by an acetamido group has been identified in the hydrolysis reactions of the *N*-acylimidazole derivatives of *N*-acetylphenylalanine and *N*-acetylvaline **69** and **70**, respectively, which reacted 100-250 fold faster than corresponding compounds which lacked an acetamido substituent.[122]



69

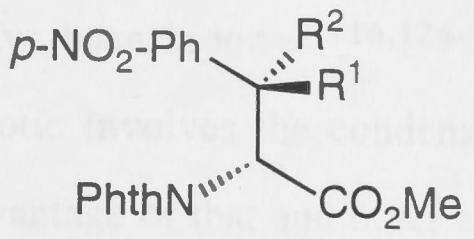


70

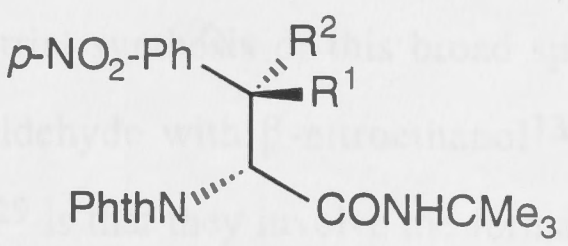
Whereas 1,5-neighbouring group participation by amido groups is common, 1,4-participation by amides is extremely rare. In the reactions of the phenylalaninamides **32a** and **32b** to give the alcohol **60**, described above, 1,4-neighbouring group participation by the amido substituent was proposed to account for the high stereoselectivity compared to that of the reactions of the corresponding bromoesters **25** and **28**.[96] Not only can participation by a neighbouring group affect the stereoselectivity of reaction, it can also affect the rate of reaction. Many reactions have been shown to occur faster when substituted with an amido group rather than with an ester.[100] Thus, it was envisaged that the effect of the neighbouring group to enhance the stereoselectivity of reaction of the phenylalanine derivatives **32a** and **32b** relative to the corresponding esters **28** and **25** could also affect the rates of the reactions. Hence, an aim of the present work was to investigate the effect of the carboxy protecting group on the rates of reactions of the phenylalanine derivatives **25**, **28**, **32a** and **32b** with aqueous silver salts in direct competitive experiments, in order to examine the importance of neighbouring group effects in these systems.

The reactions of the bromophenylalanine derivatives **25**, **28**, **32a** and **32b** are likely to proceed *via* electron deficient intermediates, due to the graded S_N1-S_N2 nature of reactions of organohalides involving silver ions.[97,98] Therefore, in order to probe the electronic nature of the neighbouring group effect in these reactions, the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** were chosen as additional substrates for the investigation, since formation of electron deficient intermediates from reactions of these substrates would be disfavoured due to the destabilising influence of the electron withdrawing nitro-substituent on those intermediates. Hence, a further aim of the work was to investigate the relative rates of reactions of the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** in competitive experiments.

In addition to investigating the electronic nature of the neighbouring group effect, the generality of the process was also of interest. The phenylalanine-derived substrates **25**, **28**, **32a**, **32b**, **71a**, **71b**, **72a** and **72b** each contain an aromatic side chain. Therefore, in order to determine the influence of the aromatic group on the neighbouring group effect the bromovaline derivatives **33** and **73** were chosen for study, since these substrates contain a non-aromatic side chain. Hence, another aim of the work was to investigate the relative rate of reactions of the valine derivatives **33** and **73** in competitive experiments.

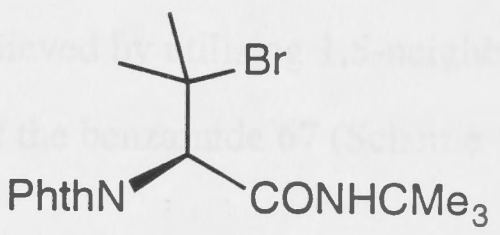


71



72

a) $R^1 = H$, $R^2 = Br$
b) $R^1 = Br$, $R^2 = H$

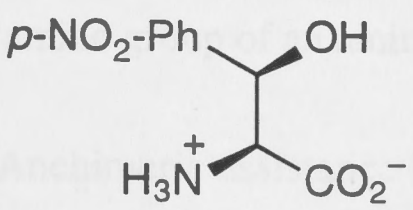


73

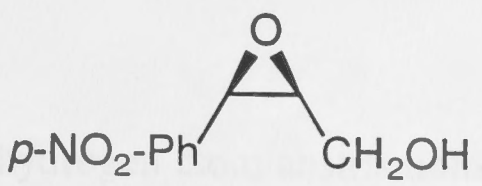
The relative stereochemistry of the alcohol **60** produced from reaction of the bromophenylalanine diastereomers **32a** and **32b** is identical to that of the natural product, chloramphenicol **54**. By analogy with that system, it was anticipated that the hydrolysis reactions of the bromonitrophenylalanine derivatives **72a** and **72b** could occur with the same relative stereochemistry. Hence, a further aim of the work described

here was to utilise the expected effect of the protected carboxy group to enhance the stereoselectivity of hydrolysis reactions of the (2*S*)-enantiomers of the bromides **72a** and **72b** in order to prepare the amino acid **74**. The racemate of the amino acid **74** has previously been elaborated to chloramphenicol **54**,[124] and therefore an enantioselective synthesis of the alcohol **74** would provide a stereocontrolled route to chloramphenicol **54**.

Chloramphenicol **54**, which was isolated in 1974 from *Streptomyces venezuelae*, was one of the first broad spectrum antibiotics to be used medicinally[125] and it is the only naturally occurring antibiotic which is economically produced on an industrial scale by synthesis rather than fermentation.[124,126,127] Various syntheses of the natural product **54** have been reported.[116,124-130] The industrial synthesis of this broad spectrum antibiotic involves the condensation of benzaldehyde with β-nitroethanol[130] but a disadvantage of that and other approaches[125,129] is that they involve the formation of racemic products which need to be resolved. An asymmetric synthesis based on azide ring-opening of the epoxide **75** has been reported.[128] Alternatively, (*S*)-phenylalanine has been used to obtain the chloramphenicol precursor **68** in a multi-step synthesis, in which diastereocontrol was achieved by utilising 1,5-neighbouring group participation in the hydrolytic rearrangement of the benzamide **67** (Scheme 18).[116]



74



75

In summary, it was envisaged that the nature of the neighbouring group effect used to explain the stereoselectivity of the hydrolysis reactions of the bromophenylalanine derivatives **25**, **28**, **32a** and **32b** could be examined through investigation of relative rates of reaction. The bromonitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** were thought to be suitable substrates to study the electronic nature of the intermediates of the reactions, while the reactions of the bromovaline derivatives **33** and **73** could be used to investigate the generality of the neighbouring group effect. Furthermore, it was anticipated that the stereoselectivity of hydrolysis of the phenylalaninamides **32a** and **32b** could be exploited with the (2*S*)-enantiomers of the nitrophenylalanine derivatives **72a** and **72b** and utilised in the stereocontrolled synthesis of the amino acid **74**, a precursor to chloramphenicol **54**. The results of these investigations are described in Chapter 2 of the Results and Discussion.

Although much less prevalent than in their ionic counterparts, neighbouring group participation is also seen in radical reactions. Anchimerically assisted bond homolyses of *ortho*-substituted aromatic peresters by neighbouring sulfide and thioether groups have been well documented.[131-135] Neighbouring group participation has been proposed by Asmus *et al.*,[136-143] in which three electron bonded species occur as intermediates, for example, in the reaction of amino acids with hydroxyl radical [$HO\therefore NH_2\text{-}CHRCO_2^-$][136] and in the radical induced oxidation of sulfides [RR'S$\therefore$OCOR"].[137-140] Coordination of sulfur atom to bromine [$R_2S\therefore Br$][141] and chlorine [$R_2SO\therefore Cl$][142] has also been demonstrated, as has a three electron bond between sulfur and phosphorus[143] and sulfur and the amino group of an amino acid.[138]

Anchimeric assistance has been observed in hydrogen atom abstractions, in the vicinal bromination of alkyl bromides[61,144-146] and in reactions of *tert*-butoxy radical with tetraethyl-silane, germane and stannane.[147] In the latter case, 1,3-participation in the hydrogen atom abstraction reaction occurs through stabilisation of the incipient radical in the transition state by the neighbouring organometallic group (MEt_3) if attack by the

tert-butoxy radical occurs *anti*- to the MEt_3 group (Figure 8). Results of studies by Wilt *et al.*[148] have also been shown[147] to illustrate neighbouring group participation in halogen transfer reactions in a similar manner.

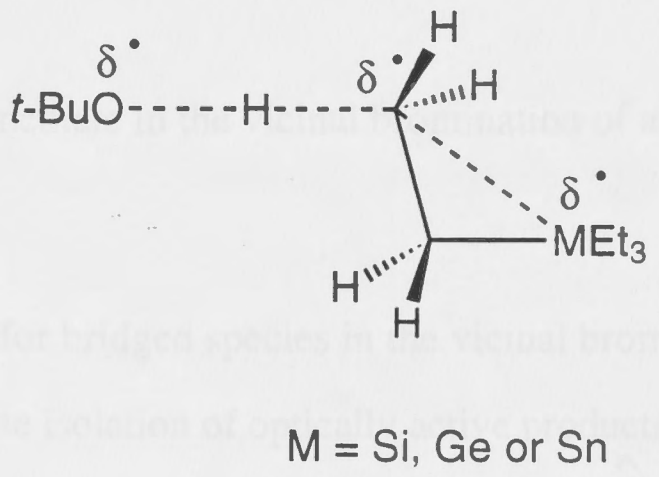


Figure 8. Hydrogen abstraction by *tert*-butoxy radical with neighbouring group participation.

Of all the examples of neighbouring group participation in radical reactions, 1,3-participation by bromine is the most common. Radical formation adjacent to an electronegative group generally is disfavoured due to inductive deactivation. In the radical bromination of alkyl bromides, however, the position adjacent to the electronegative bromo-substituent is activated toward hydrogen abstraction. An illustration of this activation is seen in the free radical bromination of alkyl bromides, which gives a preponderance of vicinal dibromides.[61] For example, bromination of bromocyclopentane afforded *trans*-1,2-dibromocyclopentane in 90% yield, while bromocyclohexane gave *trans*-1,2-dibromocyclohexane in 94% yield.[146] The regioselectivity and stereoselectivity of bromination is due to bridging by the neighbouring bromine (Figure 9),[61] which is similar to that described above for halonium ion bridging. Attack on this bridged intermediate by bromine atom from the face opposite the bonded bromine results in formation of *trans*-products in each case.

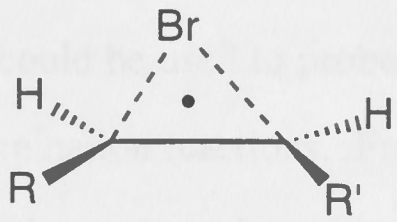
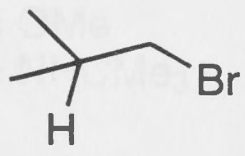


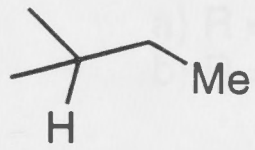
Figure 9. Bridged intermediate in the vicinal bromination of alkyl bromides.

Further evidence for bridged species in the vicinal bromination of alkyl bromides has been obtained from the isolation of optically active products, where racemic materials are expected in the absence of bridging, and from ESR studies.[149-154]

In addition to influencing the regioselectivity and stereoselectivity of bromination, neighbouring group participation by bromine can also affect the rate of hydrogen abstraction from adjacent positions. For example, tertiary hydrogen abstraction from the bromobutane **76** by bromine atom occurs approximately 8 times faster than tertiary hydrogen abstraction from 2-methylbutane **77**.[61]



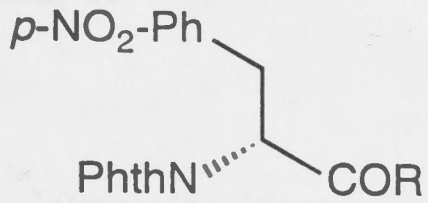
76



77

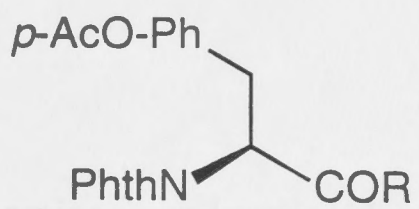
In all the examples described above involving anchimeric assistance in hydrogen atom abstraction reactions, 1,3-neighbouring group participation was involved. The analogous 1,4-neighbouring group participation has not been observed. The bromination reactions of the phenylalanine, nitrophenylalanine and tyrosine[96] derivatives **17** and **19**,

78a and **78b** and **79a** and **79b**, respectively, could involve interaction of the carboxy protecting group with the electron deficient radical intermediates. Therefore, it was envisioned that these materials could be used to probe for possible neighbouring group participation in their radical bromination reactions. Furthermore, it was anticipated that the reverse transformations of the product bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** to the corresponding reduced materials **17**, **19**, **78a**, **78b**, **79a** and **79b** using triphenyltin hydride could be utilised to investigate the possibility of neighbouring group participation, since the radical intermediates of these reactions are identical to those of the bromination reactions. As part of this investigation, it was thought that the deuterides **26**, **29**, **31a** and **31b**[58,59] could be used to determine the stereoselectivity of the hydrogen abstraction process. The results of these investigations are described in Chapter 3 of the Results and Discussion.



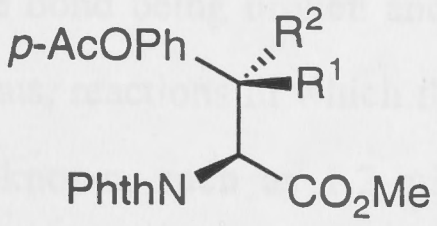
78

a) R = OMe
b) R = $NHCMe_3$



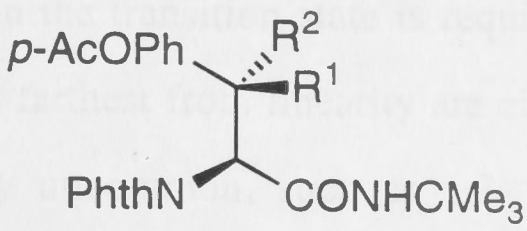
79

a) R = OMe
b) R = $NHCMe_3$



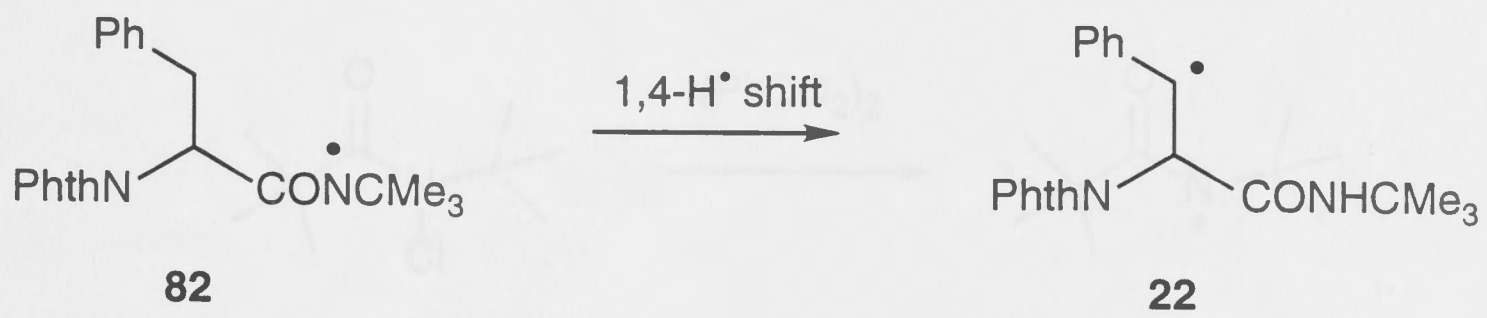
80

a) R^1 = H, R^2 = Br
b) R^1 = Br, R^2 = H



81

The work described in Chapter 3 of the Results and Discussion involves an investigation of the possibility of neighbouring group participation in intermolecular atom abstractions. In addition to the possibility of participation in intermolecular reactions, it was thought that the amido group could also be involved in intramolecular 1,4-hydrogen abstraction from the benzylic position, through reaction of the corresponding amidyl radical **82** to give the radical **22** (Scheme 19).

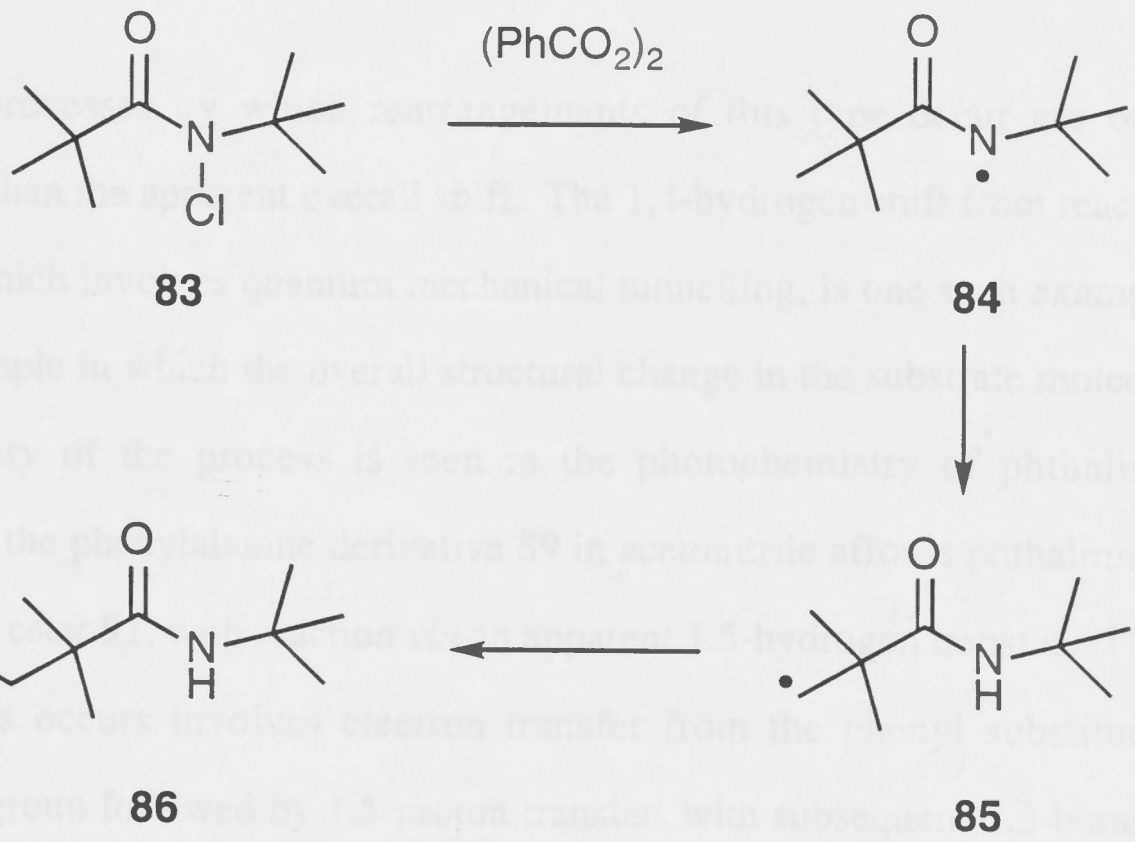


82 **22**

Scheme 19

Intramolecular atom or group transfer in radical reactions can be considered to be another type of neighbouring group participation, of which many examples have been examined previously.[155] The most commonly encountered group transfers involve 1,2-shifts, where a group such as phenyl migrates onto an adjacent atom. Hydrogen atom can also migrate, although 1,2-shifts of hydrogen appear to be unknown.[156] For intramolecular hydrogen abstraction to occur, an approximately colinear arrangement of the bond being broken and the bond being formed in the transition state is required. Thus, reactions in which the transition state deviates farthest from linearity are either unknown, such as 1,2-migration, or are extremely uncommon, such as 1,3- and 1,4-migration. 1,5-Hydrogen transfers predominate these rearrangements. Although a linear transition state can be attained in 1,6-hydrogen transfers, these occur to a much lesser extent due to entropic factors.

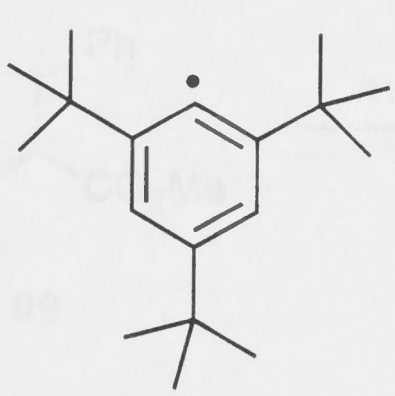
1,4-Hydrogen shifts are uncommon in solution[157-171] and do not occur unless the isomerisation is strongly exothermic.[155] A 1,4-hydrogen shift occurs upon photolysis or treatment with benzoyl peroxide of the *N*-chloroamide **83** (Scheme 20).[157] In this case, the amidyl radical **84** undergoes hydrogen migration to give the primary radical **85**, which abstracts chlorine atom to afford the β-chloride **86**. The unfavourable 1,4-shift is preferred over abstraction of hydrogen from the solvent, presumably due to steric hindrance of the amidyl radical **84**.[157]



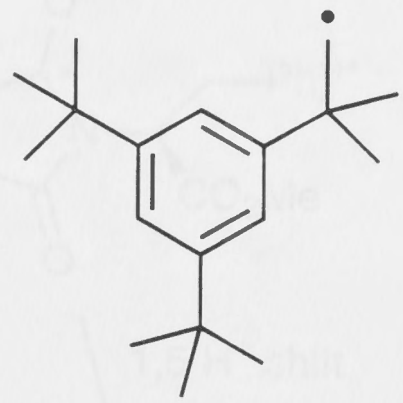
83 **84** **86** **85**

Scheme 20

1,4-Hydrogen shifts have been proposed following addition of thiyl radicals to alkenes[158-160] or alkynes.[161] The driving force in these cases has been attributed to the exothermicity of the reactions, together with the stability of the product radicals. A 1,4-shift of hydrogen has been observed in reaction of 2,4,6-tri-*tert*-butylphenyl **87**,[164,165] which involves quantum-mechanical tunnelling to give the radical **88**. In this case, unusually large deuterium kinetic isotope effects have been observed.



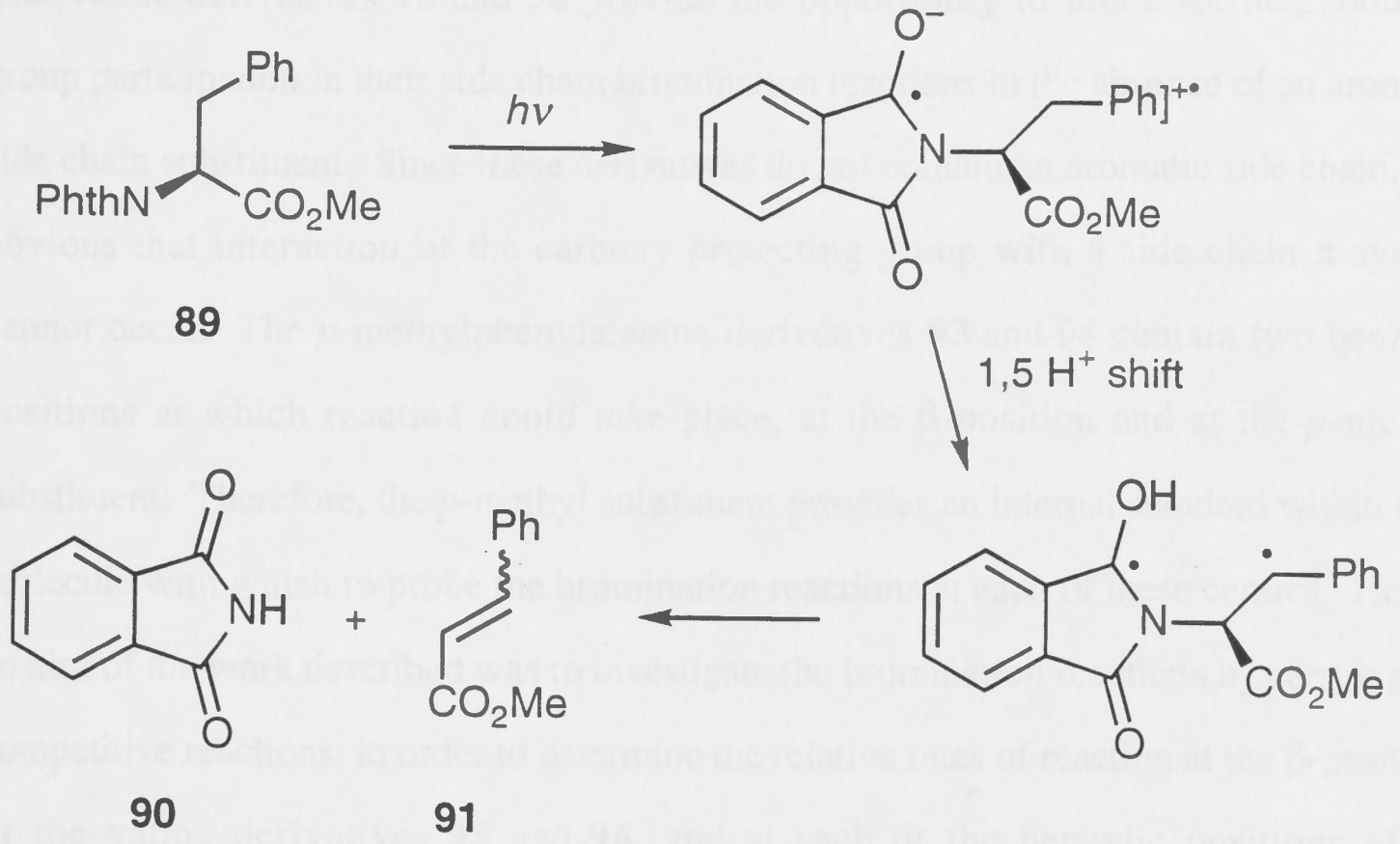
87



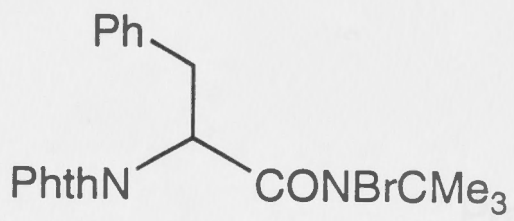
88

The processes by which rearrangements of this type occur are often more complicated than the apparent overall shift. The 1,4-hydrogen shift from reaction of the radical **87**, which involves quantum mechanical tunnelling, is one such example.[164,165] Another example in which the overall structural change in the substrate molecule belies the complexity of the process is seen in the photochemistry of phthalimides.[172] Photolysis of the phenylalanine derivative **89** in acetonitrile affords phthalimide **90** and the cinnimate ester **91**, with reaction *via* an apparent 1,5-hydrogen transfer. The process by which this occurs involves electron transfer from the phenyl substituent to the phthalimido group followed by 1,5-proton transfer, with subsequent 2,3-bond cleavage (Scheme 21).[172]

In order to investigate the possibility of intramolecular 1,4-hydrogen abstraction by the amidyl radical, the *N*-bromoamide **92** was chosen for study, anticipating that photolysis of this material would give the amidyl radical **82**, which could then undergo hydrogen abstraction, either inter- or intramolecularly, to give the β-bromide diastereomers **20a** and **20b**. The results of this investigation are described in Chapter 4 of the Results and Discussion of this thesis.



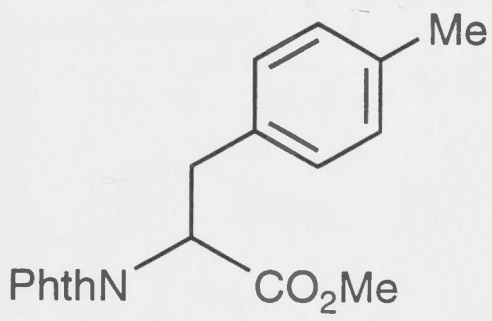
Scheme 21



92

In the work described in Chapter 3 of the Results and Discussion of this thesis, the possibility of direct interaction of the amido group with the radical centre in radical bromination reactions of phenylalanine derivatives using NBS was investigated. In addition to the possibility of direct interaction, there is also a possibility of interaction of the carboxy protecting group with the aromatic amino acid side chain in these bromination reactions. In order to investigate this possibility, the *p*-methylphenylalanine derivatives

93 and **94** and the valine derivatives **95** and **96** were thought to be suitable substrates. The valine derivatives **95** and **96** provide the opportunity to probe for neighbouring group participation in their side chain bromination reactions in the absence of an aromatic side chain substituent. Since these derivatives do not contain an aromatic side chain, it is obvious that interaction of the carboxy protecting group with a side chain π-system cannot occur. The *p*-methylphenylalanine derivatives **93** and **94** contain two benzylic positions at which reaction could take place, at the β-position and at the *p*-methyl substituent. Therefore, the *p*-methyl substituent provides an internal standard within each molecule with which to probe the bromination reactions at each of these centres. Hence, an aim of the work described was to investigate the bromination reactions by carrying out competitive reactions, in order to determine the relative rates of reaction at the β-positions of the valine derivatives **95** and **96**, and at each of the benzylic positions of the methylphenylalanine derivatives **93** and **94**.



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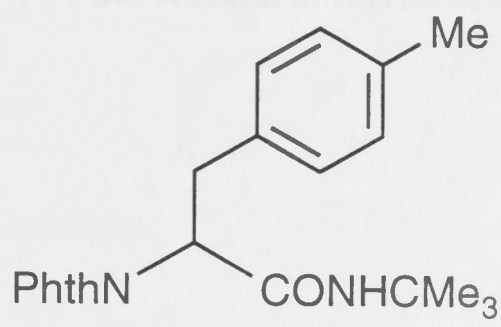

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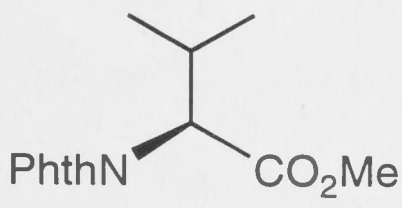
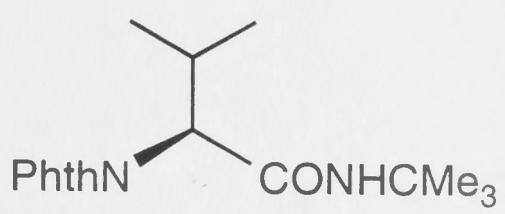


95



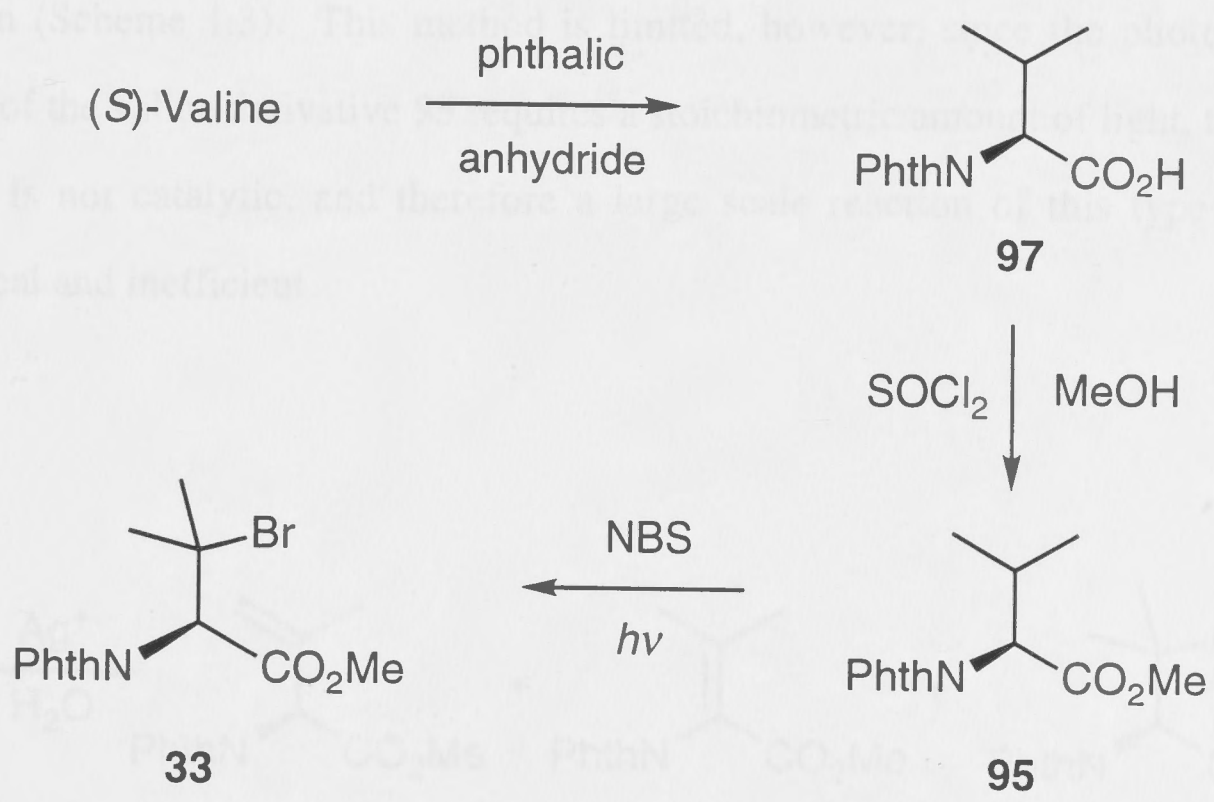
96

While the methylphenylalanine derivatives **93** and **94** could be used to investigate the possibility of interaction of the carboxy substituent in the bromination reactions using NBS, the amide **94** is of additional interest since it could be used to further investigate the possibile intramolecular 1,4-hydrogen shift in the reaction of the *N*-bromophenylalanine derivative **92**. The β-benzylic position of the methylphenylalanine derivative **94** lies within four atoms of the amido hetero-atoms, while the *p*-methyl group is situated nine atoms distant. Direct interaction of the carboxy protecting group with these centres requires a close spatial relationship, and given their position within the molecule, any such direct interaction is likely to be much greater at the β-carbon than at the *p*-methyl group, at which an intramolecular interaction cannot occur. Hence, the *p*-methyl substituents of the methylphenylalanine derivatives **93** and **94** provide internal standards within the molecules to probe for possible neighbouring group effects at both benzylic positions, and they allow further investigation into the possibility of interaction between the amido group and the aromatic moiety in the bromination processes using NBS. The results of these investigations are described in Chapter 5 of the Results and Discussion.

RESULTS AND DISCUSSION: CHAPTER 1

Stereoselective Synthesis of (2*S*,3*S*)-γ-Hydroxyvaline

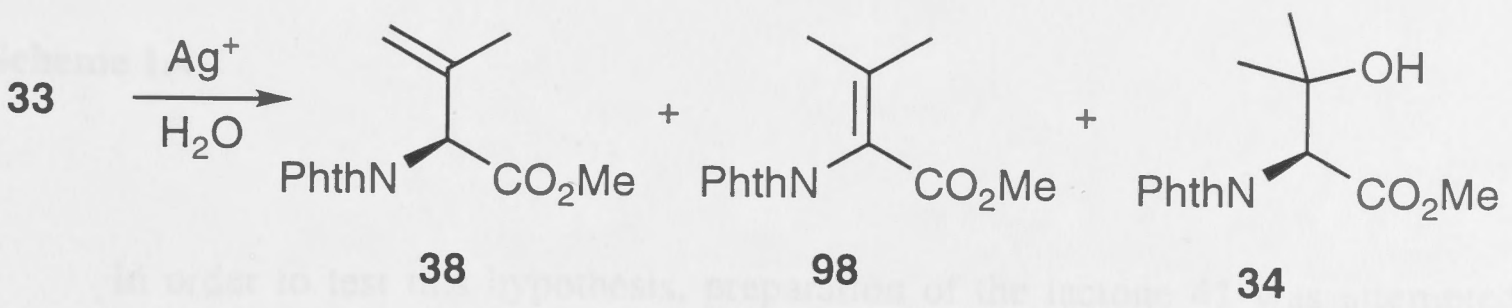
As mentioned in the Introduction of this thesis, three routes for the synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b** from (*S*)-valine were considered (Schemes 9 and 10), each of which involve reaction of the (*R*)-β-bromovaline derivative **33** to give the alkene **38**. The β-bromide **33** was synthesised from (*S*)-valine as described below (Scheme 1.1). (*S*)-Valine was protected as the *N*-phthaloyl derivative **97** by treatment with phthalic anhydride at *ca.* 150 °C, then esterified by treatment with acidified methanol. In the initial phthaloylation reaction temperature control was important, as it has been reported that racemisation can occur at temperatures above 180 °C.[173] The bromide **33** was prepared as reported previously,[54] in high yield by heating a mixture of (*S*)-*N*-phthaloylvaline methyl ester **95** and NBS at reflux in carbon tetrachloride and irradiating with a 300 W sunlamp. The



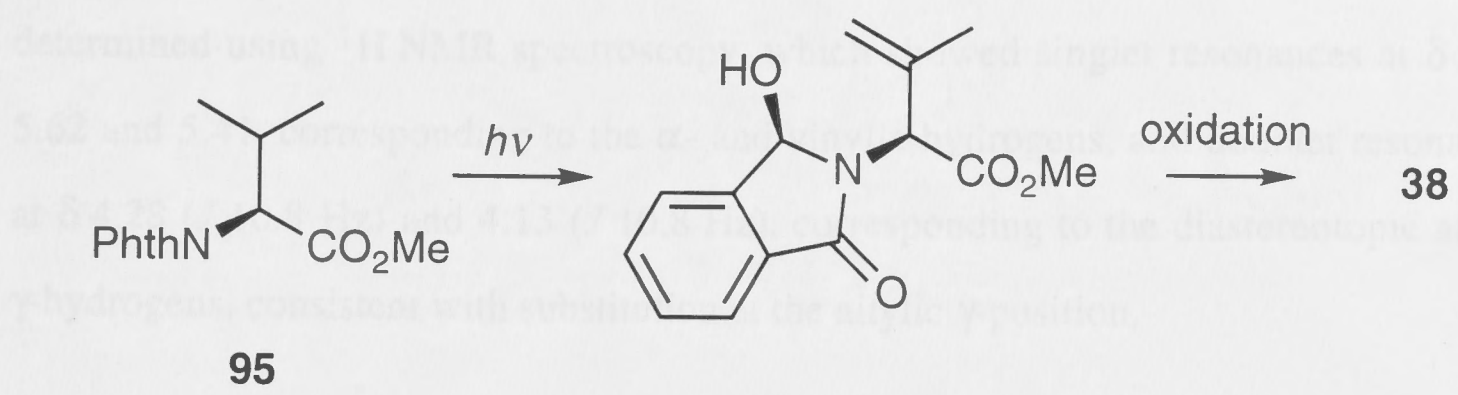
Scheme 1.1

regiospecificity of bromine incorporation was determined using ^{1}H NMR spectroscopy, which showed singlet resonances at δ 5.16, 2.15 and 1.99 corresponding to the α- and diastereotopic methyl protons, consistent with substitution at the β-position.

One procedure for the preparation of the alkene **38** involves treatment of the β-bromide **33** with silver nitrate in aqueous acetone (Scheme 1.2).[174] However, this procedure is limited since the β-hydroxyvaline derivative **34** is a major byproduct of the reaction, which was isolated in 43% yield. The α,β-alkene **98** was also produced under these conditions. In order to avoid formation of the alcohol **34**, the reaction was carried out under anhydrous conditions, by treatment of the bromide **33** with silver nitrate in dry methanol. The crude product was analysed by ^{1}H NMR spectroscopy, which showed the β,γ-alkene **38** and the α,β-alkene **98** present in the ratio *ca.* 5:1. After repeated chromatography of a portion of this mixture, the β,γ-dehydrovaline derivative **38** was isolated in 42% yield. The synthesis of the alkene **38** from the bromide **33**, described above, is complementary to that reported by Griesbeck *et al.*,[175,176] in which the alkene **38** was obtained by photolysis of the valine derivative **95**, followed by oxidation (Scheme 1.3). This method is limited, however, since the photochemical reaction of the valine derivative **95** requires a stoichiometric amount of light, that is, the reaction is not catalytic, and therefore a large scale reaction of this type becomes impractical and inefficient.



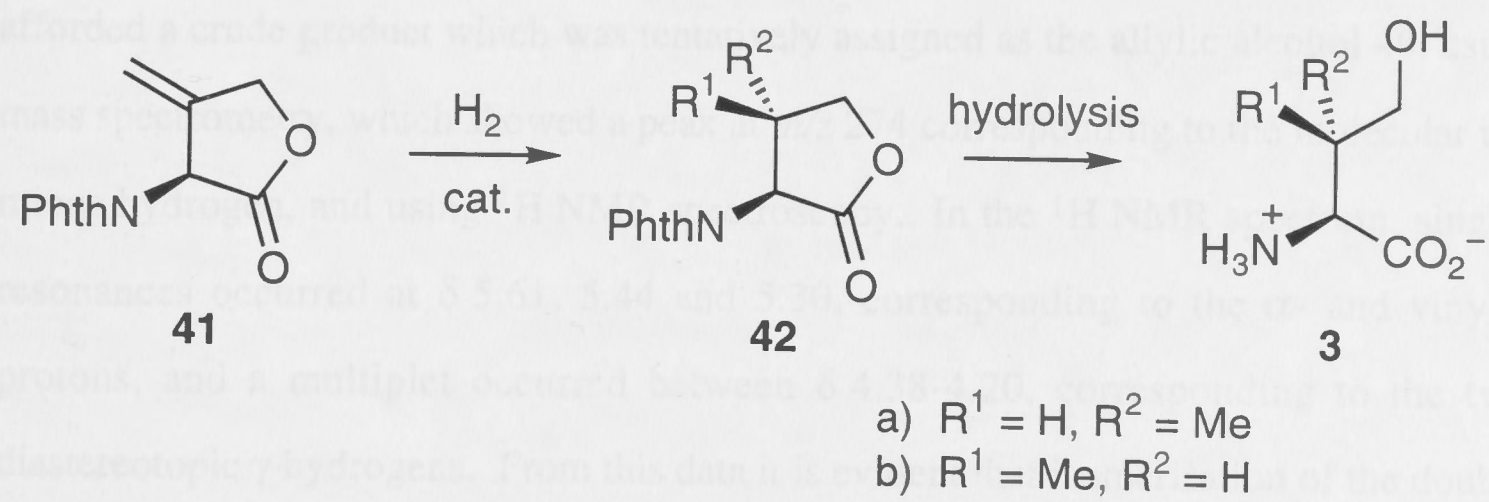
Scheme 1.2



95

Scheme 1.3

One approach considered for the stereocontrolled synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b** involved asymmetric hydrogenation of the exocyclic methylene unit of the β-methylene-γ-lactone **41**, followed by deprotection of the resultant lactones **42a** and **42b** (Scheme 1.4). In this case, it was thought that the hydrogenation would occur from the least hindered face of the exocyclic alkene **41**, thus resulting in stereoselective formation of the lactones **42a** and **42b**.

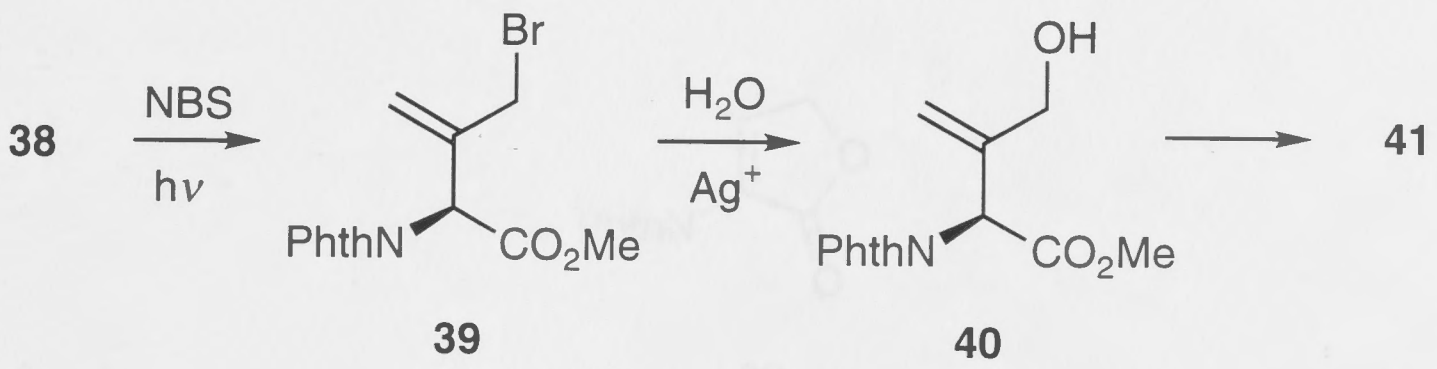


41 **42** **3**

Scheme 1.4

In order to test this hypothesis, preparation of the lactone **41** was attempted using the sequence shown below (Scheme 1.5). Treatment of the alkene **38** with NBS under photolytic conditions afforded the allylic bromide **39**, in 80% yield after

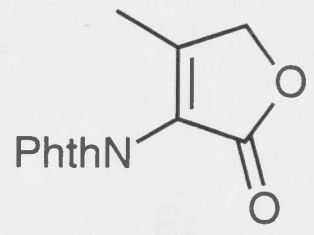
purification by chromatography on silica. The regioselectivity of reaction was determined using ^{1}H NMR spectroscopy, which showed singlet resonances at δ 5.72, 5.62 and 5.41, corresponding to the α- and vinylic hydrogens, and doublet resonances at δ 4.28 (*J* 10.8 Hz) and 4.13 (*J* 10.8 Hz), corresponding to the diastereotopic allylic γ-hydrogens, consistent with substitution at the allylic γ-position.



Scheme 1.5

Hydrolysis of the allylic bromide **39** using aqueous silver nitrate in acetone afforded a crude product which was tentatively assigned as the allylic alcohol **40**, using mass spectrometry, which showed a peak at *m/z* 274 corresponding to the molecular ion minus hydrogen, and using ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum, singlet resonances occurred at δ 5.61, 5.44 and 5.30, corresponding to the α- and vinylic protons, and a multiplet occurred between δ 4.38-4.20, corresponding to the two diastereotopic γ-hydrogens. From this data it is evident that isomerisation of the double bond to give an α,β-unsaturated system did not occur during the reaction. Purification of the alcohol **40** was attempted using chromatography on silica, however only the lactone **99** was eluted. It was established that lactone formation had occurred by analysis of the product using mass spectrometry, which showed a peak at *m/z* 243 corresponding to the molecular ion. Isomerisation to the α,β-unsaturated system was determined using ^{1}H NMR spectroscopy, which showed singlet resonances at δ 4.95

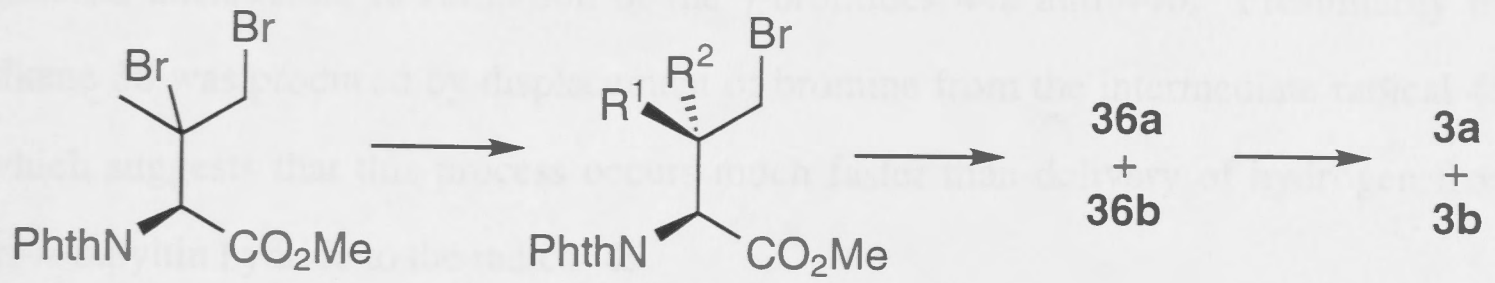
and 2.13, corresponding to the methylene and methyl protons, respectively, consistent with a non-terminal alkene moiety. Consistent with this observation, an absence of peaks in the region *ca.* δ 5.0-6.0 indicated that there were no α- or vinylic protons present in the molecule, and consequently none of the lactone **41**. Presumably, the alcohol **40** lactonised and isomerised during chromatography due to the acidic conditions on silica.



99

In an attempt to avoid lactonisation of the alcohol **40** during chromatography, less acidic conditions were used. The chromatographic process was repeated using 1% and then 5% triethylamine in the eluant, however, in each case the lactone **99** was isolated and neither the alcohol **40** nor exocyclic alkene **41** were detected. Thus, since none of the exocyclic alkene **41** was detected in the crude products from the reactions nor isolated following chromatography using these conditions, it appears that isomerisation of the double bond occurs immediately upon lactonisation of the alcohol **40**. In addition to using triethylamine in the eluant to reduce the acidity of the chromatography conditions, purification of the alcohol **40** using basic alumina was also attempted. Under these conditions decomposition occurred and neither the alcohol **40** nor the lactones **41** and **99** were isolated. Therefore, given the difficulties encountered in the purification of the alcohol **40** and isolation of the lactone **41**, the synthesis of the γ-hydroxyvaline isomers **3a** and **3b** using this procedure was not continued.

A second approach considered for the synthesis of the γ-hydroxyvaline isomers **3a** and **3b** involves reduction of the dibromide **43** using tri-*n*-butyltin hydride to give the γ-bromides **44a** and **44b**, which could be hydrolysed to the corresponding alcohols **36a** and **36b** and deprotected (Scheme 1.6). In addition, since the reduction of the dibromide **43** is likely to proceed *via* the radical **45**, it was thought that delivery of hydrogen to the radical **45** could occur stereoselectively due to 1,2-stereoinduction, thus providing a stereocontrolled route to the γ-hydroxyvaline isomers **3a** and **3b**.



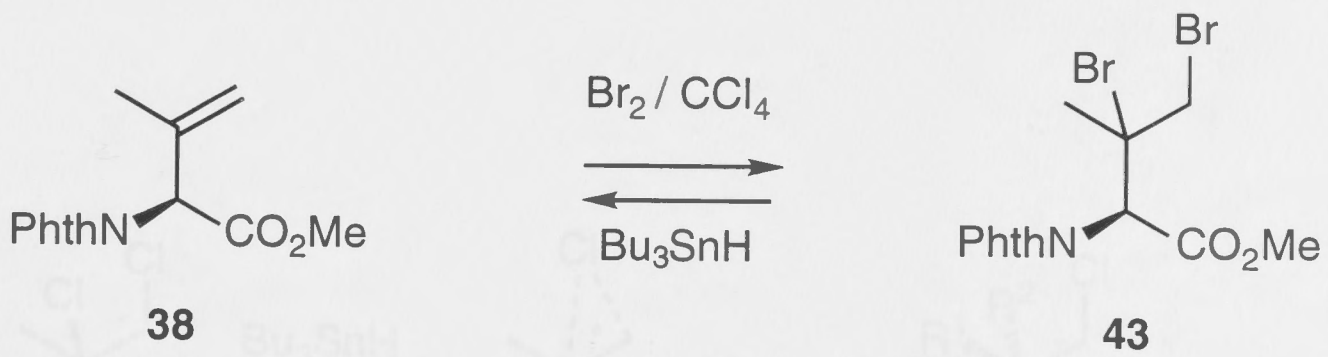
43 **44**

a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H

Scheme 1.6

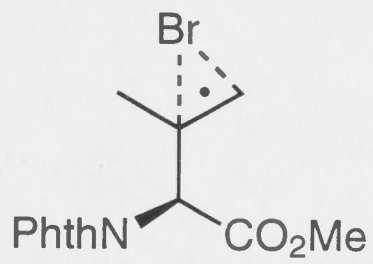
In order to test this hypothesis, synthesis of the dibromide **43** was required. It was anticipated that electrophilic addition of bromine to the alkene **38** would give the dibromide **43**. Hence, the alkene **38** was treated with a solution of bromine in carbon tetrachloride. Under these conditions, a crude product was obtained which was tentatively identified as a *ca.* 3:1 mixture of diastereomers of the dibromide **43** (Scheme 1.7). Formation of a dibromide species from the reaction was determined from the mass spectrum of the crude product, which showed peaks at *m/z* 418, 420 and 422 in the ratio 1:2:1 corresponding to the molecular ion, whilst the regioselectivity of reaction was determined using ^{1}H NMR spectroscopy. Singlet resonances at δ 5.49 and 2.02

were attributed to the α- and methyl protons, while peaks at δ 4.73 (d, *J* 10.7 Hz) and 3.91 (d, *J* 10.7 Hz) were attributed to the diastereotopic γ-hydrogens of the major isomer of the dibromide **43**. Similarly, signals corresponding to the α- and methyl protons were observed at δ 5.61 and 2.13, whilst peaks at δ 4.63 (d, *J* 10.7 Hz) and 3.98 (d, *J* 10.7 Hz) were attributed to the diastereotopic γ-hydrogens of the minor isomer of the dibromide **43**. The dibromide **43** was unstable and was therefore used in the subsequent reaction without further purification and characterisation. Treatment of the crude dibromide **43** with tri-*n*-butyltin hydride afforded the alkene **38** as the major product (Scheme 1.7). There were no peaks in the ^{1}H NMR spectrum of the crude material attributable to formation of the γ-bromides **44a** and **44b**. Presumably the alkene **38** was produced by displacement of bromine from the intermediate radical **45**, which suggests that this process occurs much faster than delivery of hydrogen from tri-*n*-butyltin hydride to the radical **45**.



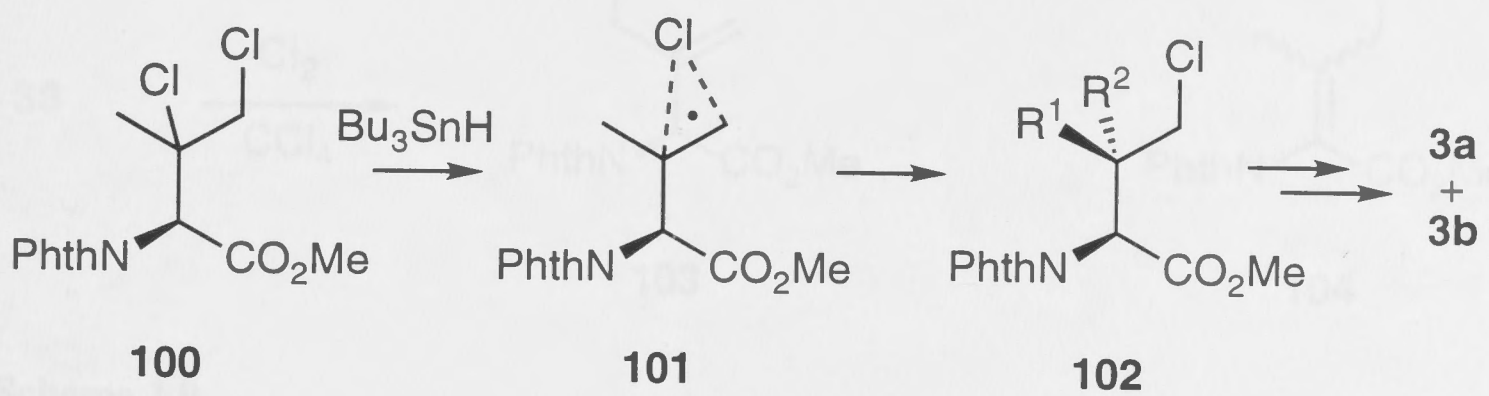
38 **43**

Scheme 1.7



45

As a method for introducing functionality at the γ-position, reduction of the dibromide **43** was unsuccessful. Hence, a variation of this approach was considered. It was anticipated that chlorine functionality could be introduced at the γ-position, by reduction of the dichloride **100** with tri-*n*-butyltin hydride to give the γ-chloride **102** *via* the radical **101** (Scheme 1.8). Given the greater strength of the chlorine–carbon bond relative to that of the bromine–carbon bond, it was anticipated that cleavage of the former bond would be less likely to occur and therefore addition of hydrogen to the radical **101** to give the γ-chlorides **102a** and **102b** (Scheme 1.8) would occur in preference to cleavage of this bond. In addition to allowing the introduction of functionality at the γ-position, this approach is of further interest due to the possibility of stereoselectivity as a result of 1,2-stereoinduction, using the same reasoning as described above for the reaction of the dibromide **43** with tri-*n*-butyltin hydride. Hydrolysis of the γ-chlorides **102a** and **102b** to the alcohols **36a** and **36b** followed by deprotection could therefore provide a stereocontrolled synthesis of the γ-hydroxyvaline isomers **3a** and **3b**.

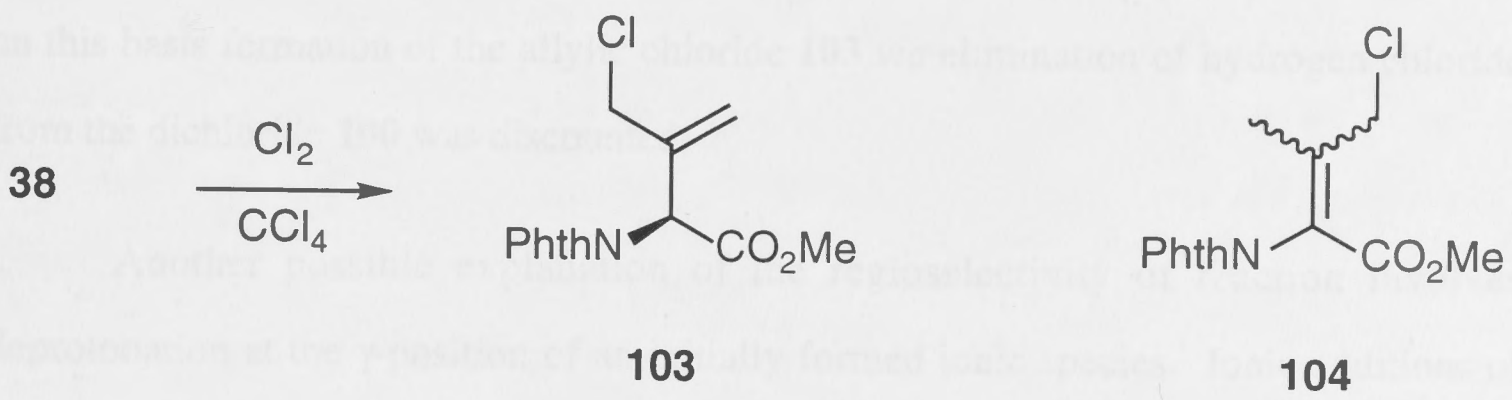


100 **101** **102**

a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H

Scheme 1.8

In order to investigate this hypothesis, synthesis of the dichloride **100** was required. It was envisioned that the dichloride **100** could be produced in an analogous manner to that used to prepare the dibromide **43**, by treatment of the alkene **38** with a solution of chlorine in carbon tetrachloride. However, treatment of the alkene **38** with chlorine in carbon tetrachloride afforded the allylic chloride **103**, which was isolated in 54% yield after chromatography on silica (Scheme 1.9). The regioselectivity of chlorination was determined using ^{1}H NMR spectroscopy, which showed singlet resonances at δ 5.68, 5.59 and 5.42, corresponding to the α- and vinylic hydrogens, respectively, and doublets at δ 4.37 (*J* 12.1 Hz) and 4.22 (*J* 12.1 Hz), corresponding to the diastereotopic γ-protons, consistent with substitution at the allylic γ-position. There were no peaks in the ^{1}H NMR spectrum of the crude material attributable to formation of the dichloride **100** or the allylic chloride isomer **104.** Since the dichloride **100** was not produced, synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b** using this method was not pursued further.



Scheme 1.9

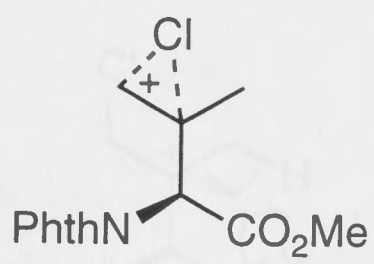
The regioselectivity of chlorination of the alkene **38** is identical to that seen in the bromination of the alkene **38** using NBS (Scheme 1.5), which suggested that the allylic chloride **103** is produced by a radical mechanism. In comparison, ionic bromination of the alkene **38** using molecular bromine occurs to give the dibromide **43**

(Scheme 1.7). While the addition of a halogen such as bromine to an unsaturated system generally occurs *via* an ionic mechanism, radical addition can occur in the presence of a radical initiator such as light. Although an initiator was not used in the reaction of the alkene **38** with chlorine, initiation of a radical process could occur with ambient light. To investigate this possibility, the reaction was carried out in the dark and in the presence of hydroquinone, a radical scavenger, since a radical reaction under these conditions would be unlikely to occur. Using these conditions the allylic chloride **103** was produced in identical proportions as in the previous reaction, as determined through analysis of the crude product using ^{1}H NMR spectroscopy. This result suggests that the allylic chloride **103** is produced *via* an ionic mechanism.

One possible mechanism to account for the regioselectivity of reaction involves addition of chlorine to the alkene **38** to give the dichloride **100**, which then undergoes elimination of hydrogen chloride to give the allylic chloride **103**. However, it has already been shown that the alkene **38** reacts with bromine to give the dibromide **43**. This material is likely to be more susceptible to elimination of the halogen than the dichloride **100** due to the greater leaving group ability of bromide to chloride ion, and on this basis formation of the allylic chloride **103** *via* elimination of hydrogen chloride from the dichloride **100** was discounted.

Another possible explanation of the regioselectivity of reaction involves deprotonation at the γ-position of an initially formed ionic species. Ionic additions of halogens such as iodine or bromine to unsaturated systems are known to occur *via* bridged halonium ions (Figure 7).[100-102] In comparison with reactions of iodine and bromine, halonium ion formation from chlorine addition to alkenes occurs to a lesser extent, such that the more substituted end of the ion possesses much greater carbonium ion character.[104] As a consequence of unsymmetrical bridging in the chloronium ion system, hydrogens on carbons adjacent to the carbonium ion centre are likely to be more acidic than those adjacent to a bridged halonium ion species. Therefore, it is

likely that the intermediate in the reaction of the alkene **38** with chlorine resembles the non-bridged tertiary carbocation **106**, rather than the bridged species **105**, from which deprotonation is likely to occur readily.



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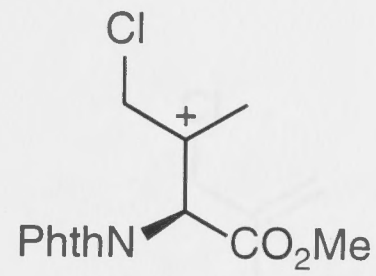


106

One species present in the reaction which could act as a base to remove a proton from the γ-position of the intermediate **106** is chloride ion. Statistically, a 1:3 ratio of the α,β-alkene **104** and the allylic chloride **103** would be expected, since removal of the α-hydrogen or one of the three methyl protons could occur. However, in the ^{1}H NMR spectrum of the crude reaction mixture the allylic chloride **104** was not detected. Although steric hindrance by the bulky phthaloyl and methoxycarbonyl substituents to approach of chloride ion to the α-proton could affect reaction at this site, removal of the α-proton would still be expected to occur. Hence, this result suggests that the regioselectivity of reaction is not due to deprotonation at the γ-position by chloride ion.

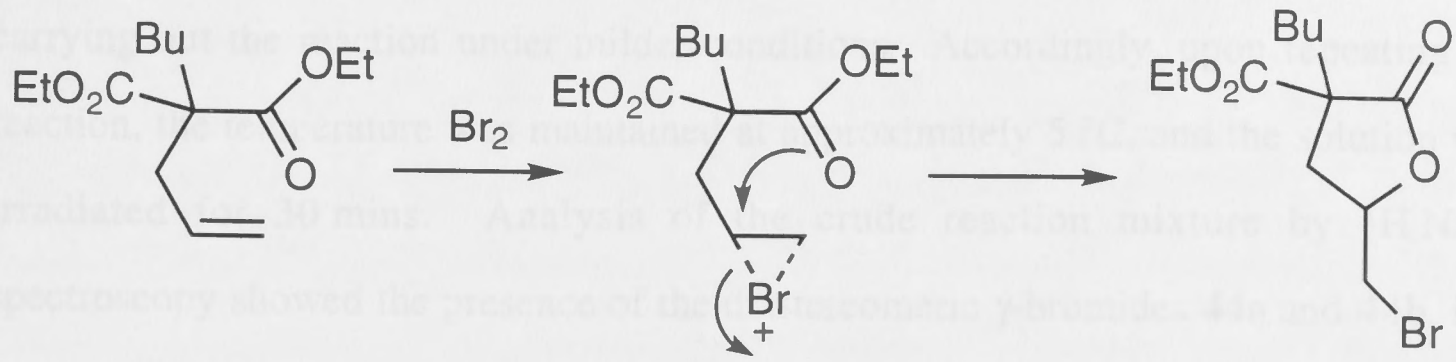
Alternatively, the methoxycarbonyl substituent could act as an intramolecular base to remove a γ-proton (Scheme 1.10). Reaction in this manner would account for the regioselectivity of reaction and the absence of the chloride **104**. In this process a favourable six-membered transition state is involved. Presumably, the analogous process involving removal of the α-hydrogen by the ester group, resulting in formation

of the chloride **104**, does not occur since this would involve the less favourable four membered transition state. Hence, the regioselectivity of reaction together with an absence of the chloride isomer **104** is consistent with a mechanism involving intramolecular deprotonation by the carboxy group.

106 **103**

Scheme 1.10

Intramolecular reaction of the carboxy group in the chlorination reaction of the alkene **38** is similar to that in halolactonisation reactions. Halolactonisation generally involves the conversion of a β,γ- or γ,δ-unsaturated carboxylic acid into a halolactone, although derivatives such as esters are also known to react in this manner.[3,104,177-182] Halolactonisation occurs with intramolecular nucleophilic attack at an intermediate halonium ion by a carboxy group, an example of which is shown in Scheme 1.11.[177,178] For the analogous process to occur in the reaction of the alkene **38** with chlorine, nucleophilic attack at the tertiary centre by the carboxy group is required. This would produce a strained four membered ring, which is unfavourable, and therefore deprotonation at the γ-position to give affording the allyl chloride **103** prevails.



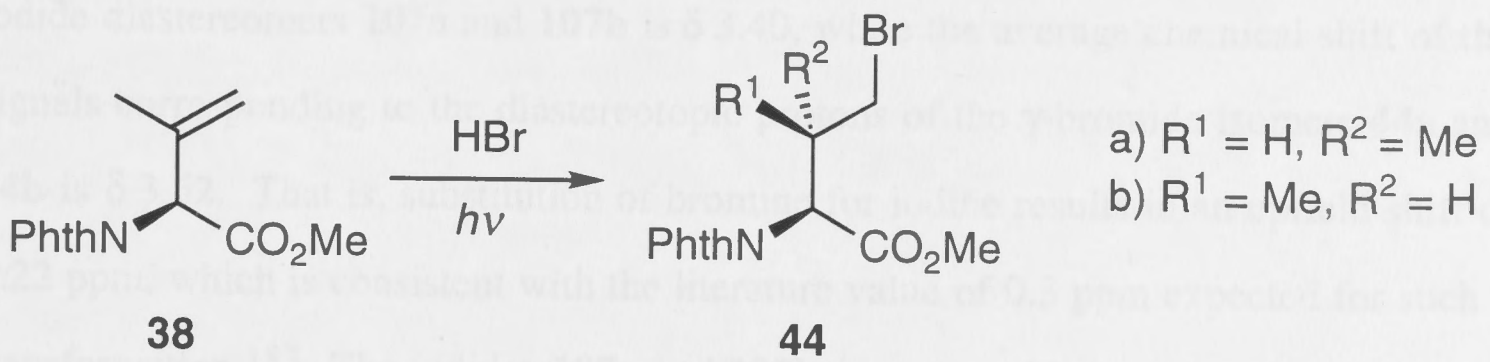
Scheme 1.11

In summary, the alkene **38** reacts with chlorine to give the allylic chloride **103** *via* an ionic mechanism. The regioselectivity of reaction and absence of the isomer **104** in the crude mixture is consistent with neighbouring group participation by the carboxy group to deprotonate the intermediate **106** at the γ-position.

Given that the attempts to prepare the γ-bromides **44a** and **44b** and the γ-chlorides **102a** and **102b** from the corresponding dihalides **43** and **100** were unsuccessful, synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b** *via* an alternative route was investigated. The third approach considered for the synthesis of the γ-hydroxyvaline isomers **3a** and **3b** involved *anti*-Markovnikov radical addition of hydrogen bromide to the alkene **38**, followed by hydrolysis. In addition to introducing bromine functionality at the less hindered end of the alkene moiety, *anti*-Markovnikov addition of hydrogen bromide to the alkene **38** is of further interest due to the possibility of 1,2-stereoinduction, as outlined previously.

The addition of hydrogen bromide to the alkene **38** was initially attempted by passing a dry stream of the gas through a solution of the alkene **38** in carbon tetrachloride for 10 mins, then heating the solution for 2 h at reflux and irradiating with a 300 W sunlamp. Analysis of the crude product using ^{1}H NMR spectroscopy showed that decomposition had occurred, presumably due to the vigorous conditions used in the

reaction. Therefore, it was anticipated that decomposition could be minimised by carrying out the reaction under milder conditions. Accordingly, upon repeating the reaction, the temperature was maintained at approximately 5 °C, and the solution was irradiated for 30 mins. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed the presence of the diastereomeric γ-bromides **44a** and **44b**, in a 2.2:1 ratio (Scheme 1.12). The regioselectivity of hydrogen bromide addition to the alkene **38** was determined from the ^{1}H NMR spectrum of the isomeric mixture. Doublet resonances occurred at δ 5.02 (*J* 8.4 Hz) and 1.03 (*J* 6.9 Hz), which correspond to the α- and methyl hydrogens, respectively, while doublet of doublet resonances at δ 3.90 (*J* 5.1 and 10.2 Hz) and 3.66 (*J* 3.9 and 10.2 Hz) correspond to the diastereotopic γ-hydrogens of the major diastereomer **44a**. In addition, doublets occurred at δ 4.91 (*J* 7.4 Hz) and 1.30 (*J* 6.6 Hz), corresponding to the α- and methyl hydrogens, respectively, while doublet of doublet resonances occurred at δ 3.65 (*J* 3.7 and 10.3 Hz) and 3.25 (*J* 6.8 and 10.3 Hz), which correspond to the diastereotopic γ-protons of the minor isomer **44b**. The ^{1}H NMR spectral data are consistent with substitution at the γ-position. The diastereomers **44a** and **44b** were inseparable using chromatography on silica and the crude mixture was therefore used without purification.



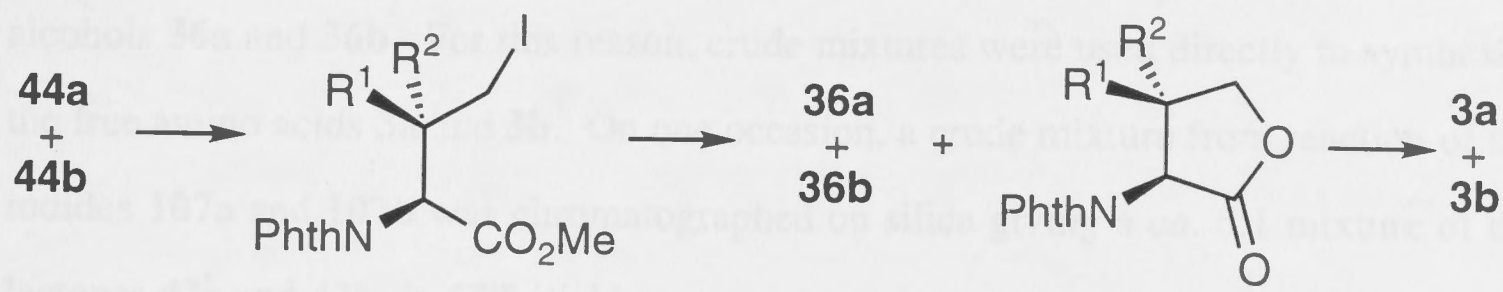
38 **44**

Scheme 1.12

Hydrolysis of the bromides **44a** and **44b** to the corresponding alcohols **36a** and **36b** was attempted initially by treatment with aqueous silver nitrate in acetone both at room temperature and at reflux but no reaction occurred. Given the lack of reactivity in this system, alternative methods to facilitate the substitution process were considered. It was anticipated that the use of a more powerful nucleophile or a better leaving group would favour the substitution process. The most obvious choice of a nucleophile more powerful than water is hydroxide ion, however, the sensitivity of the molecule to basic conditions precluded this treatment. Hence, conversion of the bromo-substituent to a better leaving group was envisioned.

Iodide ion is a better leaving group than bromide ion, hence conversion of the bromides **44a** and **44b** to the corresponding iodides **107a** and **107b** was performed. Accordingly, the bromides **44a** and **44b** were treated with sodium iodide in acetone at reflux. Under these conditions, the corresponding iodides **107a** and **107b** were produced (Scheme 1.13). Iodo substitution was confirmed from the ^{1}H NMR spectrum, which contained doublet of doublets at δ 3.63 (*J* 5.4 and 10.2 Hz) and 3.50 (*J* 3.9 and 10.2 Hz) corresponding to the diastereotopic γ-hydrogens of the major isomer **107a**, and doublet of doublets at δ 3.47 (*J* 3.8 and 10.2 Hz) and 3.01 (*J* 7.8 and 10.2 Hz) corresponding to the diastereotopic γ-hydrogens of the minor isomer **107b**. The average chemical shift of the signals corresponding to the diastereotopic protons of the iodide diastereomers **107a** and **107b** is δ 3.40, while the average chemical shift of the signals corresponding to the diastereotopic protons of the γ-bromide isomers **44a** and **44b** is δ 3.62. That is, substitution of bromine for iodine results in an upfield shift of 0.22 ppm, which is consistent with the literature value of 0.3 ppm expected for such a transformation.[183] The iodides **107a** and **107b** were unstable and therefore the crude product was used in the subsequent reaction without further purification.

Hydrolysis of the crude iodides **107a** and **107b** was achieved by treatment with silver nitrate in aqueous acetone, which gave a mixture containing the lactone **42a** and the alcohols **36a** and **36b**. Acidic hydrolysis of the mixture, followed by purification by ion exchange chromatography, gave a 3:1 mixture of the γ-hydroxyvaline diastereomers **3a** and **3b**, in 60% yield from the γ-bromides **44a** and **44b** (Scheme 1.13). The ^{1}H NMR spectral data for the diastereomers **3a** and **3b** are consistent with literature values.[22] The major isomer **3a** was separated from this mixture by fractional crystallisation.



107 **42**

a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H

Scheme 1.13

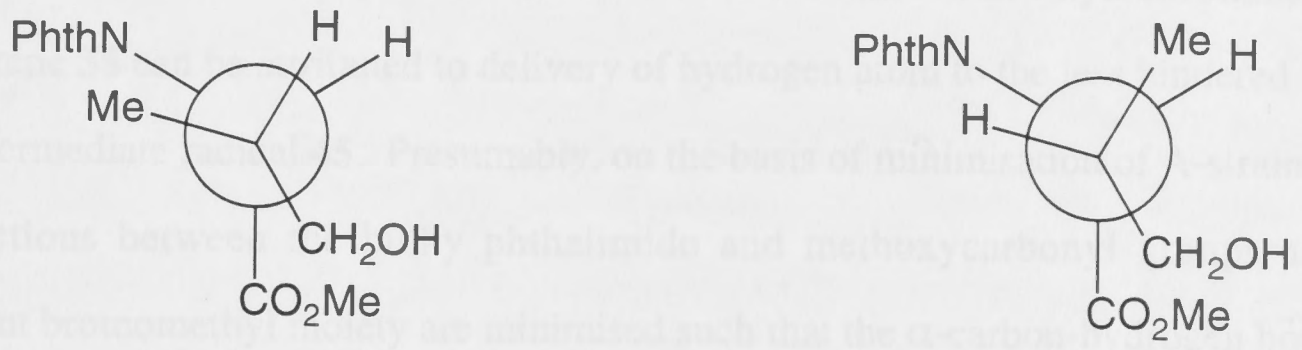
The relative stereochemistry of the γ-hydroxyvaline diastereomers **3a** and **3b** is apparent from comparison of their ^{1}H NMR spectral data with literature values.[22] In the ^{1}H NMR spectrum of the mixture of isomers **3a** and **3b**, doublet resonances occur at δ 0.94 (*J* 7.2 Hz) and 1.02 (*J* 7.0 Hz), which correspond to the methyl protons of the major isomer **3a** and the minor isomer **3b**, respectively. The chemical shifts of the signals corresponding to the methyl groups of the isomers **3a** and **3b** are in close agreement with literature data,[22] in which that signal of the (2*S*,3*S*)-isomer **3a** occurred at δ 0.97, and at δ 1.04 for the (2*S*,3*R*)-diastereomer **3b**. The absolute stereochemistry

of the alcohols **3a** and **3b** was confirmed by the optical rotation of the diastereomer **3a**.[22] The literature values[22] for the specific rotation of the (2*S*,3*S*)-isomer **3a** and the (2*S*,3*R*)-diastereomer **3b** are +23.3° and +26.4°, respectively, while those of the corresponding (2*R*,3*R*)- and the (2*R*,3*S*)-enantiomers of **3a** and **3b** are –22.7° and –26.9°. The specific rotation obtained for the synthesised material in this work was +24.0°, which indicates that this material contains (2*S*)-stereochemistry, and is in close agreement with the value reported for the (2*S*,3*S*)-diastereomer **3a**.

Repeated reactions of the iodides **107a** and **107b** with aqueous silver nitrate afforded various mixtures of the lactones **42a** and **42b** and the alcohols **36a** and **36b** (Scheme 1.13), which were difficult to separate due to incomplete lactonisation of the alcohols **36a** and **36b**. For this reason, crude mixtures were used directly to synthesise the free amino acids **3a** and **3b**. On one occasion, a crude mixture from reaction of the iodides **107a** and **107b** was chromatographed on silica giving a *ca.* 6:1 mixture of the lactones **42a** and **42b**, in 67% yield.

The relative stereochemistry of the lactone diastereomers **42a** and **42b** was determined using a nuclear Overhauser experiment. In the ^{1}H NMR spectrum, signals due to the H3, H4, H5 and H5' protons of the lactone **42b** occur at δ 5.01 (d, *J* 10.0 Hz), 3.06-2.90 (m), 4.66 (dd, *J* 8.4 and 8.7 Hz) and 4.26 (dd, *J* 8.0 and 8.7 Hz), respectively. Irradiation of the resonance centred at δ 2.98 affected the signals at δ 5.01 by +27%, at δ 4.66 by +0.2% and at δ 4.26 by -4.0%. The H3 and H5 protons of the lactone **42a** give rise to a multiplet at δ 4.66, while the H4 and H5' proton signals of that compound occur at δ 3.27-3.11 (m) and 3.98 (dd, *J* 9.2 and 10.3 Hz), respectively. Irradiation of the resonance centred at δ 3.19 affected the signals at δ 4.66 by +5.5% and at δ 3.98 by -1.7%. These values indicate that interactions between the adjacent H3 and H4 protons of the (3*S*,4*R*)-isomer **42b** are larger than for the (3*S*,4*S*)-isomer **42a**, and can be attributed to a *syn*-relationship between the H3 and H4 protons of the isomer **42b**.

Presumably, the production of the 6:1 mixture of the lactones **42a** and **42b** from reaction of a 2.2:1 mixture of the iodides **107a** and **107b** is a consequence of selective lactonisation of the alcohol **36a**. This is in accord with the relative stereochemistry of the alcohols **36a** and **36b**. In the eclipsed conformation required for lactonisation, unfavourable steric interactions exist between the phthalimido and methyl substituents of the (2*S*,3*S*)-isomer **36b** (Figure 1.1). In contrast, these unfavourable interactions are not present for the (2*S*,3*R*)-isomer **36a** (Figure 1.1), and therefore lactonisation of the (2*S*,3*S*)-alcohol **36a** occurs in preference to reaction of the (2*S*,3*R*)-isomer **36b.**



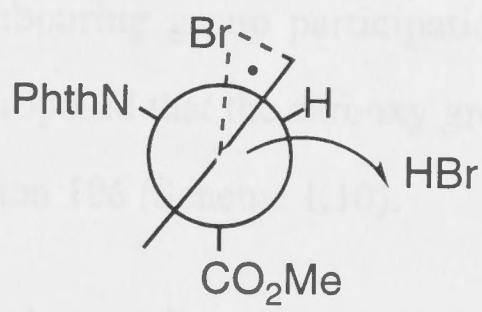
36b **36a**

Figure 1.1. Eclipsed conformations of the alcohols **36a** and **36b** required for lactonisation.

To determine the stereochemistry of the major isomer of the γ-bromides **44a** and **44b**, the mass balance of the reactions of the bromides **44a** and **44b** to give the free amino acids **3a** and **3b**, *via* the iodides **107a** and **107b** and the lactones **42a** and **42b**, was considered. In the 2.2:1 mixture of the diastereomers of the bromides **44a** and **44b** used in the initial reaction, there was *ca.* 1.91 mmol of the major isomer and *ca.* 0.87 mmol of the minor isomer present. Using this mixture, the maximum theoretical yield of the free amino acid isomers **3a** and **3b** is 1.91 mmol (254 mg) and 0.87 mmol (115 mg), respectively. The free amino acids **3a** and **3b** (223 mg, 1.68 mmol) were isolated as a 3:1 mixture, which corresponds to 1.26 mmol (167 mg) of the isomer **3a**

and 0.42 mmol (56 mg) of the isomer **3b**. Therefore, since the amount of the isomer **3a** in this mixture is greater than the maximum theoretical yield of the minor isomer **3b**, it is clear that the major isomer **3a** is produced from the bromide **44a**. Similarly, it is clear that the major iodide **107a** is derived from the predominant bromide **44a**, and it is the iodide **107a** which affords the lactone **42a**. As expected, therefore, the stereochemistry of the lactone **42a** corresponds to that of the γ-hydroxyvaline isomer **3a**. Using the same reasoning, the stereochemistry of the bromides **44a** and **44b** and the iodides **107a** and **107b** may be inferred from that of the alcohols **3a** and **3b**.

The stereoselectivity which arises in the *anti*-Markovnikov hydrobromination of the alkene **38** can be attributed to delivery of hydrogen atom to the less hindered face of the intermediate radical **45**. Presumably, on the basis of minimisation of A-strain, steric interactions between the bulky phthalimido and methoxycarbonyl groups and the adjacent bromomethyl moiety are minimised such that the α-carbon-hydrogen bond, the β-carbon and the bromomethyl substituent are approximately coplanar (Figure 1.2). In this configuration, delivery of hydrogen atom to the least hindered face of the radical **45**, opposite to the bulky phthalimido moiety, results in formation of the (2*S*,3*S*)-bromide **44a**. Stereoselective formation of the (2*S*,3*S*)-bromide **44a** is consistent with the stereochemistry of the major isomer of the lactone **42a** and the amino acid **3a** which also possess the (2*S*,3*S*)-stereochemistry.



45

Figure 1.2. Preferred conformation of the radical **45**.

In order to determine the absolute stereochemistry of the natural product, γ-hydroxyvaline was isolated from the plant species *Kalanchoe daigremontiana* using the procedure of Pollard *et al.*,[82] which is outlined below. The lyophilised leaves and stems of the plant were stirred vigorously in water for 48 h, then the mixture was filtered. The filtrate was then washed with chloroform and evaporated to dryness, and the residue was purified by ion exchange chromatography using Amberlite IR-120 (NH_4^+). The crude material was recrystallised from acetone and water, then analysed using ^{1}H NMR spectroscopy. By comparison of the ^{1}H NMR spectral data of the isolated material with that of the synthesised isomers **3a** and **3b** and by spiking with a sample of a 3:1 mixture of the isomers **3a** and **3b** of the synthetic material, the natural product was determined to be identical to the synthetic (2*S*,3*S*)-isomer **3a**. In the spiking experiment, a sample of the natural product was added to the synthetic material and an enhancement of the signals corresponding to the major isomer **3a** was observed. The relative and absolute stereochemistry of the natural product was confirmed by X-ray crystallographic analysis (Appendix 4), from which the (2*S*,3*S*)-stereochemistry was apparent. Consequently the synthesis described involving anti-Markovnikov hydrobromination of the alkene **38** constitutes a stereoselective synthesis of the natural isomer **3a**.

In summary, as part of an attempted synthesis of the γ-hydroxyvaline diastereomers **3a** and **3b**, the reaction of the alkene **38** with chlorine resulted in formation of the allylic chloride **103**. The mechanism of formation of this species was investigated, in which neighbouring group participation by the carboxy protecting group was implicated. It is proposed that the carboxy group acts as a base to remove a proton from the intermediate ion **106** (Scheme 1.10).

In addition, the γ-hydroxyvaline isomers **3a** and **3b** have been prepared stereoselectively from (*S*)-valine. The stereoselectivity in this process was achieved *via* 1,2-asymmetric induction, as a result of minimised A-strain by the intermediate radical

45, in the *anti*-Markovnikov radical hydrobromination of the β,γ-dehydrovaline derivative **38**. The relative and absolute stereochemistry of the γ-hydroxyvaline isomers **3a** and **3b** was determined using a variety of methods, including a nuclear Overhauser enhancement experiment with the diastereomeric lactones **42a** and **42b**. The synthetic material **3a** was shown to be identical to the natural product, which was isolated from the plant species *Kalanchoe daigremontiana*. The structure of the natural product was confirmed through X-ray crystallographic analysis (Appendix 4). This approach has the potential to be applied to the stereocontrolled synthesis of a variety of hydroxy amino acids.

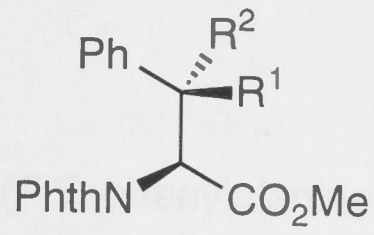
RESULTS AND DISCUSSION: CHAPTER 2

Neighbouring Group Effects in Side Chain Substitution Reactions of Amino Acid Derivatives: A Stereocontrolled Route to Chloramphenicol

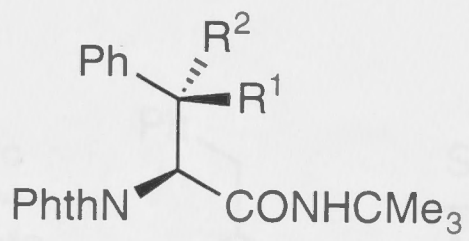
In the previous Chapter, the reaction of the dehydrovaline derivative **38** with chlorine to give the allylic chloride **103** was discussed, in which a mechanism involving neighbouring group participation by the carboxy group acting as a base to deprotonate the intermediate **106** was proposed to account for the regioselectivity of reaction. The effect of the neighbouring carboxy group to influence the regiochemistry of reaction in this manner is complementary to that proposed in the reactions of the bromophenylalanine derivatives **25** and **28**, and **32a** and **32b** to give the alcohols **55** and **56**, and **60**, respectively,[60,96] in which the stereoselectivity of reaction was markedly affected by the nature of that group. The apparent effect of the neighbouring carboxy group on the stereoselectivity of these reactions prompted an investigation into the rates of reactions, through competitive experiments, which are the subject of discussion in this Chapter. In order to investigate the generality of the neighbouring group effect and the dependence on the nature of the amino acid side chain, the valine derivatives **33** and **73** and the nitrophenylalanine derivatives **71a** and **71b**, and **72a** and **72b** were chosen for study. In these studies, the effect of the carboxy group on the rates and course of reactions was investigated. In addition, it was anticipated that the influence of the neighbouring carboxy group on the stereoselectivity of reactions of bromophenylalanine derivatives could be exploited in the synthesis of the β-hydroxy-nitrophenylalanine derivative **74**, a precursor to chloramphenicol **54**.

In the present work, the racemic analogues **18a** and **18b**, and **20a** and **20b** of the (*S*)-phenylalanine derived bromides **25** and **28**, and **32a** and **32b** were used for convenience. The racemic bromides **18a** and **18b**, and **20a** and **20b** were prepared using standard procedures as described below. The bromovaline derivative **33** was

prepared as described in the previous Chapter, while the synthesis of the amide **73** is described herein. The (*R*)-nitrophenylalanine derived bromides **71a** and **71b**, and **72a** and **72b** were prepared using standard procedures, as were the corresponding racemic and (*S*)-nitrophenylalanine derived analogues. The amino acid derivatives referred to herein are racemic unless otherwise indicated.



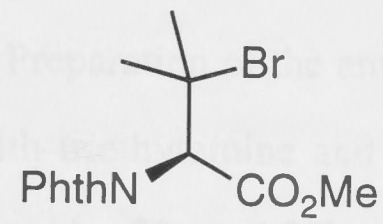
18



20

a) $R^1 = H$, $R^2 = Br$
b) $R^1 = Br$, $R^2 = H$

(stereochemical descriptors show relative stereochemistry only)



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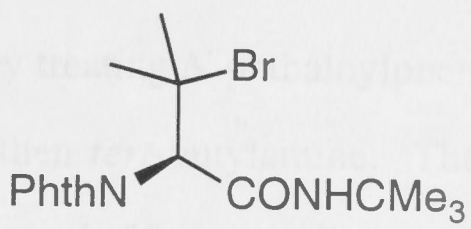
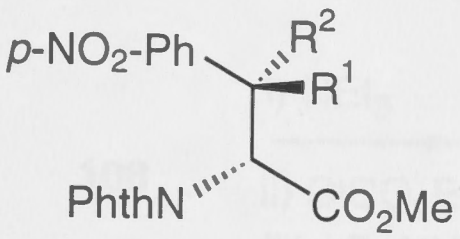
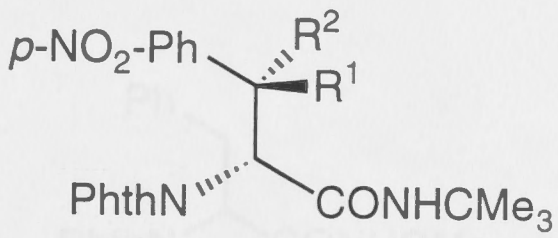


73



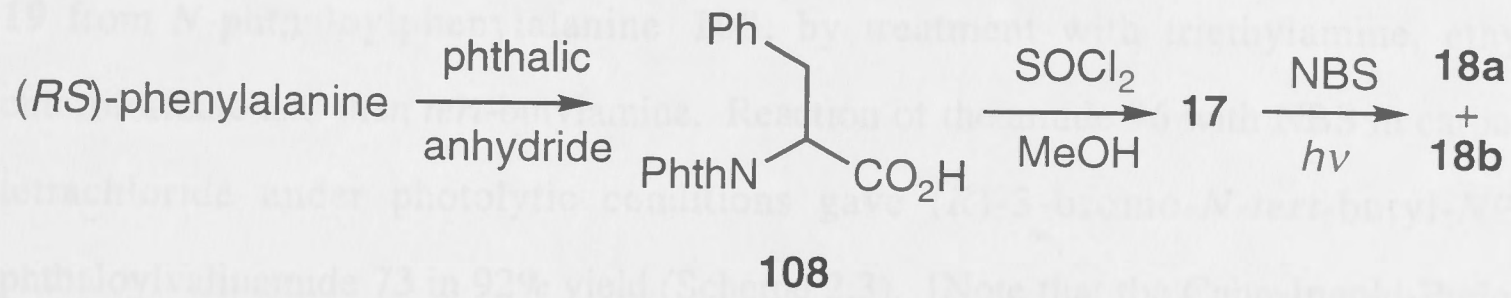
71



72

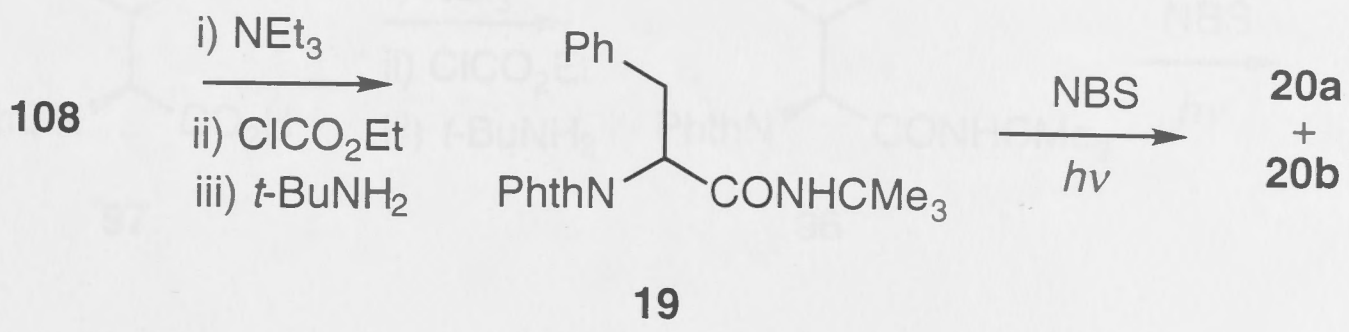
a) $R^1 = H$, $R^2 = Br$
b) $R^1 = Br$, $R^2 = H$

Treatment of phenylalanine with phthalic anhydride gave *N*-phthaloyl-phenylalanine **108**, in 90% yield (Scheme 2.1). *N*-Phthaloylphenylalanine methyl ester **17** was prepared in 90% yield from the acid **108**, by treatment with acidified methanol. The racemic bromoesters **18a** and **18b** were prepared as a 1:1 mixture, by treatment of the ester **17** with NBS for 2 h in carbon tetrachloride and irradiation from a 300 W sunlamp, and isolated in quantitative yield (Scheme 2.1).



Scheme 2.1

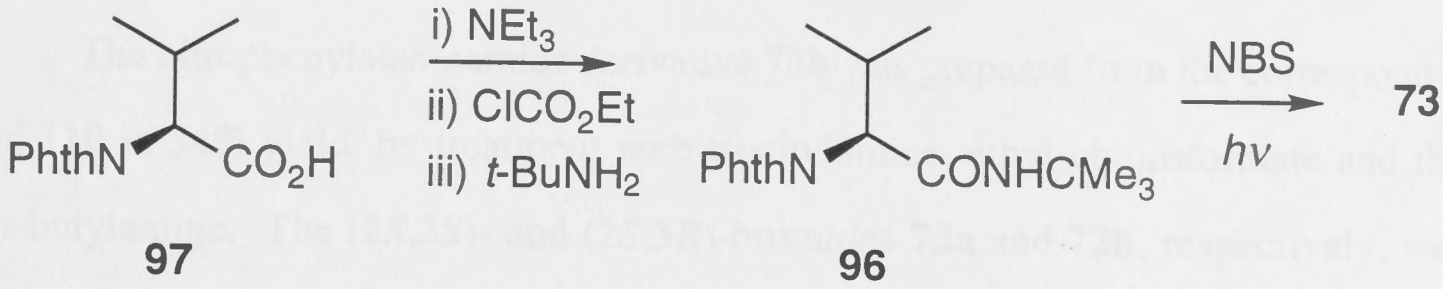
Preparation of the amide **19** was achieved by treating *N*-phthaloylphenylalanine **108** with triethylamine and ethyl chloroformate, then *tert*-butylamine. The racemic bromoamides **20a** and **20b** were prepared from the amide **19** in a similar manner to that described above for the preparation of the bromoesters **18a** and **18b**, by treatment with NBS under photolytic conditions (Scheme 2.2).



Scheme 2.2

The relative stereochemistry of the bromoesters **18a** and **18b** and the bromoamides **20a** and **20b** is apparent from their ^{1}H NMR spectral data. The ^{1}H NMR spectral data for these materials are identical to those reported for the corresponding (2*R*,3*R*)- and (2*R*,3*S*)-bromides **25** and **32b**, and **28** and **32a**,[59] which show a general trend.[59,96]

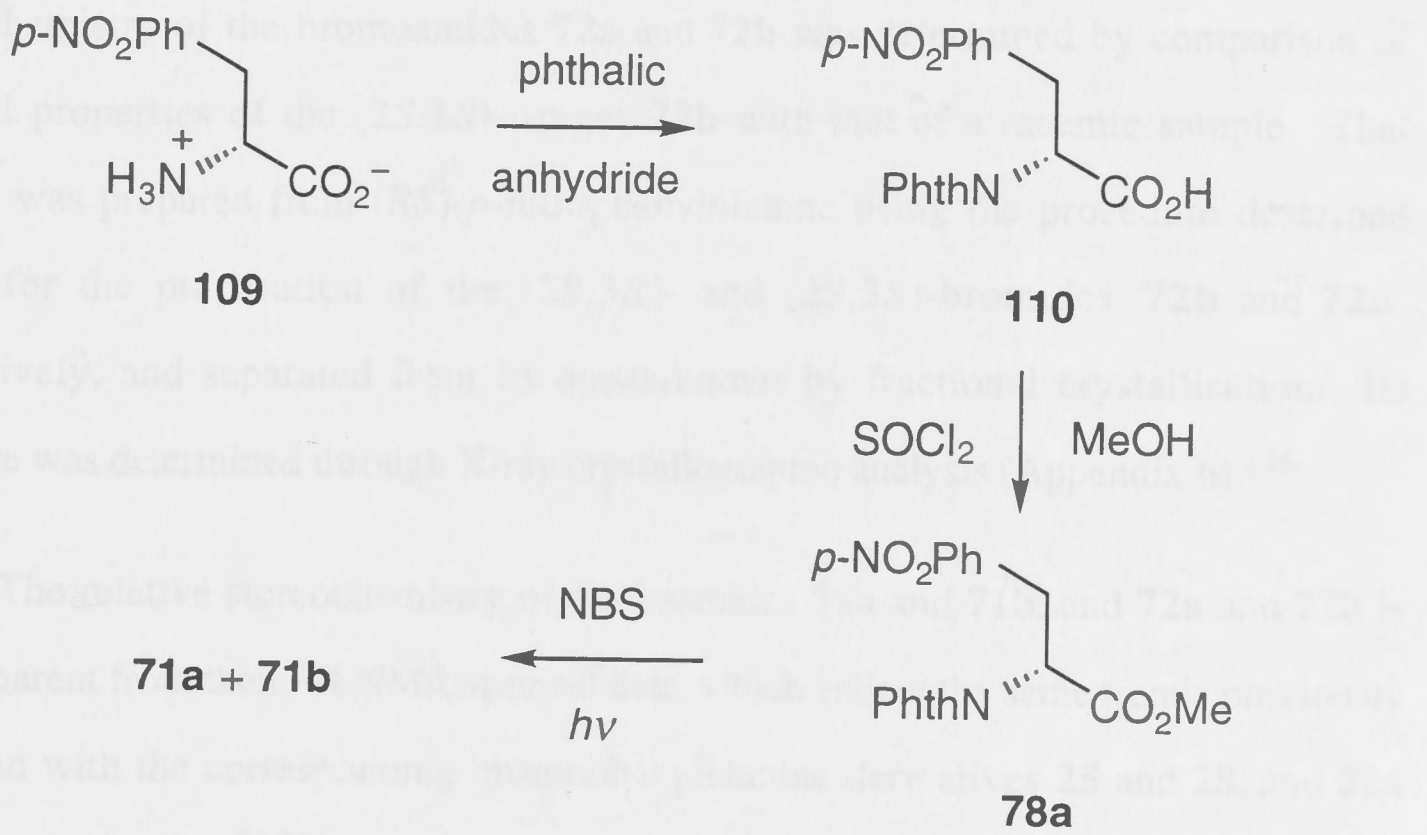
The valinamide **96** was prepared from (*S*)-*N*-phthaloylvaline **97** using an identical procedure to that described above for the preparation of the phenylalaninamide **19** from *N*-phthaloylphenylalanine **108**, by treatment with triethylamine, ethyl chloroformate and then *tert*-butylamine. Reaction of the amide **96** with NBS in carbon tetrachloride under photolytic conditions gave (*R*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloylvalinamide **73** in 92% yield (Scheme 2.3). [Note that the Cahn-Ingold-Prelog designation at the α-carbon of the bromides **18a**, **18b**, **20a**, **20b**, **33**, **71a**, **71b**, **72a**, **72b** and **73** is reversed by comparison with that of the corresponding non-halogenated amino acid derivatives **17**, **19**, **78a**, **78b**, **95** and **96**, due to the change in priority of the substituents.] The regiochemistry of reaction was determined from the ^{1}H NMR spectrum, which contained singlet resonances at δ 5.28, 2.07 and 1.86, corresponding to the α-proton and the two diastereotopic methyl groups, respectively, consistent with substitution at the β-position.



97 **96**

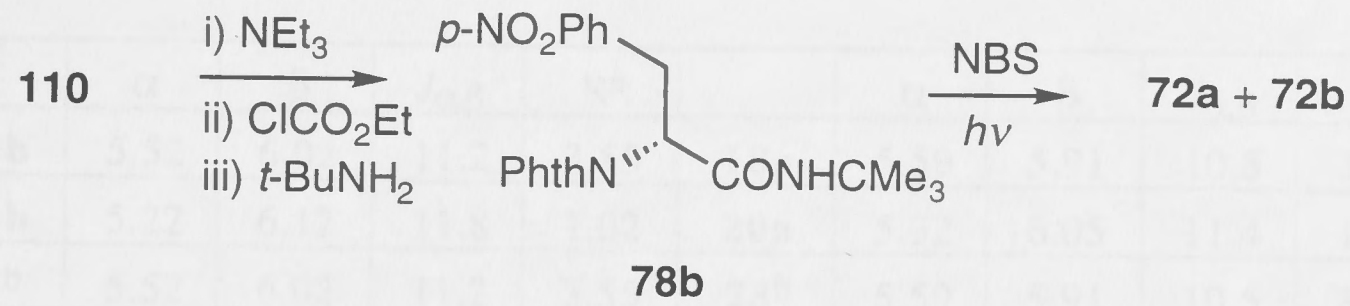
Scheme 2.3

(*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine **110** was prepared in 97% yield using a literature procedure,[184] by heating a mixture of (*R*)-*p*-nitrophenylalanine **109** monohydrate, triethylamine and phthalic anhydride in toluene at reflux for 3 h in a flask which was fitted with a Dean-Stark apparatus. Treatment of this material with acidified methanol gave the ester **78a** in 86% yield after recrystallisation of the crude product from a mixture of dichloromethane and light petroleum. Treatment of the ester **78a** with NBS in carbon tetrachloride for 4 h gave a 1:1 mixture of the (2*S*,3*S*)- and (2*S*,3*R*)-bromides **71a** and **71b**, respectively, in quantitative yield (Scheme 2.4).



Scheme 2.4

The nitrophenylalaninamide derivative **78b** was prepared from the corresponding acid **110** in 54% yield, by treatment with triethylamine, ethyl chloroformate and then *tert*-butylamine. The (2*S*,3*S*)- and (2*S*,3*R*)-bromides **72a** and **72b**, respectively, were prepared as a 1:1 mixture from the amide **78b**, by photolysis with NBS in a 4:1 mixture of carbon tetrachloride and dichloromethane for 3 h, and isolated in 98% yield (Scheme 2.5).



78b

Scheme 2.5

The stereochemistry of the bromides **71a** and **71b** was determined through X-ray crystallographic analysis of the (2*S*,3*R*)-isomer **71b** (Appendix 5),[185] whilst the stereochemistry of the bromoamides **72a** and **72b** was determined by comparison of spectral properties of the (2*S*,3*R*)-isomer **72b** with that of a racemic sample. That sample was prepared from (*RS*)-*p*-nitrophenylalanine using the procedure described above for the preparation of the (2*S*,3*R*)- and (2*S*,3*S*)-bromides **72b** and **72a**, respectively, and separated from its diastereomer by fractional crystallisation. Its structure was determined through X-ray crystallographic analysis (Appendix 6).[186]

The relative stereochemistry of the bromides **71a** and **71b**, and **72a** and **72b** is also apparent from their ^{1}H NMR spectral data, which follow the same trends previously observed with the corresponding bromophenylalanine derivatives **25** and **28**, and **32a** and **32b** (Table 2.1).[59,96] The signals corresponding to the carboxy protecting groups occur at lower chemical shift for the diastereomers **71a** and **72a** than for the corresponding diastereomers **71b** and **72b**, while the diastereomers **71a** and **72a** exhibit the β-proton signal at higher chemical shift, the α-proton signal at lower chemical shift, and a larger coupling constant between the α- and β-protons, than for the corresponding diastereomers **71b** and **72b**.

	α	β	$J_{\alpha,\beta}$	R[a]		α	β	$J_{\alpha,\beta}$	R[a]
18b	5.52	6.02	11.2	3.55	**18a**	5.59	5.91	10.5	3.82
20b	5.22	6.17	11.8	1.02	**20a**	5.32	6.05	11.4	1.40
25[b]	5.52	6.02	11.2	3.55	**28**[b]	5.59	5.91	10.5	3.82
32b[b]	5.22	6.17	11.8	1.02	**32a**[b]	5.32	6.05	11.4	1.40
71a	5.51	6.02	11.2	3.59	**71b**	5.59	5.97	10.3	3.83
72a	5.19	6.20	11.7	1.11	**72b**	5.29	6.18	11.4	1.41

[a] R values correspond to the signals of the carboxy protecting group.

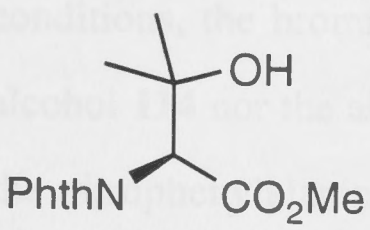
[b] Data from reference 59.

Table 2.1. ^{1}H NMR spectral data for the bromides **18a**, **18b**, **20a**, **20b**, **25**, **28**, **32a**, **32b**, **71a**, **71b**, **72a** and **72b**.

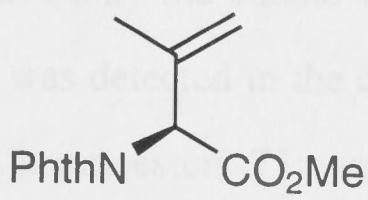
Under comparable conditions to those used in the preparation of the bromophenylalanine derivatives **18a**, **18b**, **20a** and **20b** from the corresponding non-brominated analogues **17** and **19**, the nitro-substituted analogues **78a** and **78b** required longer to react. The rate of reaction of each substrate with NBS reflects the ease with which hydrogen is transferred from that substrate to bromine atom and is consistent with the transition state proposed for radical bromination in which hydrogen transfer to electrophilic bromine atom occurs with the development of a partial positive charge at the site of hydrogen abstraction (Figure 1). In the reactions of the nitrophenylalanine derivatives **78a** and **78b**, radical formation occurs with the development of a partial positive charge adjacent to the electron deficient nitro-aromatic moiety, which is unfavourable. Consequently, the nitrophenylalanine derivatives **78a** and **78b** require longer to react than the corresponding phenylalanine derivatives **17** and **19**.

As described in the Introduction of this thesis, reaction of a 1:1 mixture of the bromophenylalanine derivatives **25** and **28** with aqueous silver nitrate affords the alcohols **55** and **56** in a 5:1 ratio (Scheme 14).[60] In separate experiments, the bromoester **25** reacted to give a 2:1 mixture of the alcohols **55** and **56**, with retention of stereochemistry being the dominant process, while the isomer **28** gave only the inverted alcohol **55**. By comparison, under identical conditions to those used in the reactions of the bromoesters **25** and **28**, each of the bromoamides **32a** and **32b** reacts to give only the alcohol **60** (Scheme 16).[96]

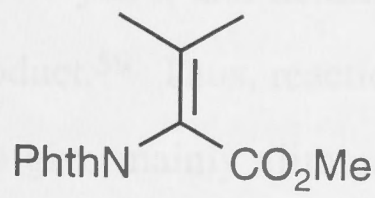
By comparison with the bromophenylalanine derivatives **25** and **28**, and **32a** and **32b**, which react solely by substitution, the reaction of the bromovaline derivative **33** with aqueous silver nitrate in acetone occurs with competing substitution and elimination. Thus, under these conditions the bromide **33** reacted to give a crude product containing the β-hydroxyvaline derivative **34** and the dehydrovaline derivatives **98** and **38** (Scheme 1.2), in the ratio *ca.* 3.5 : 1 : 3.5. Chromatography of the mixture afforded the alcohol **34** in 43% yield, and the alkenes **98** and **38**, in yields of 8 and 34%, respectively. In comparison, when treated with aqueous silver nitrate under identical conditions, the bromoamide **73** reacted to give a *ca.* 2:1 mixture of the alcohol **111** and the alkene **112**, from which the components were isolated in 63% and 26% yield, respectively (Scheme 2.6). The ^{1}H NMR spectrum of the crude product of the reaction of the valinamide **73** showed no indication of formation of the α,β-alkene **113**.



34



38



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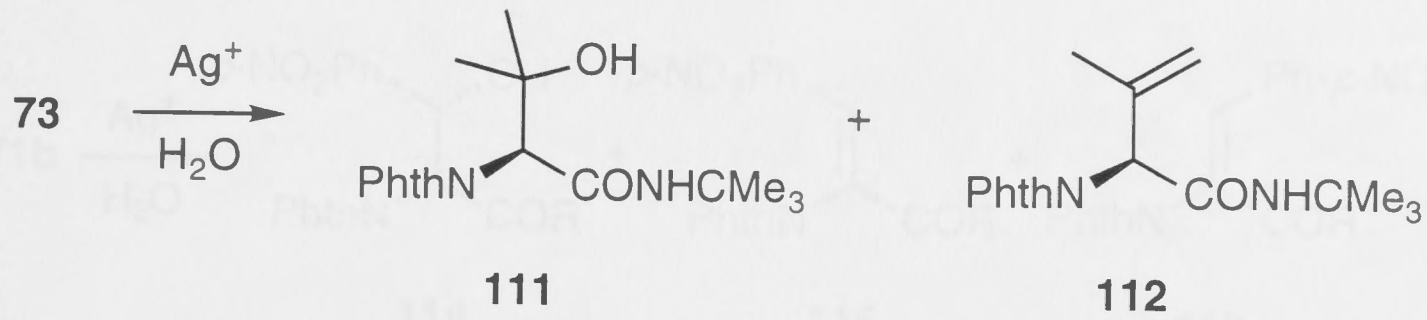
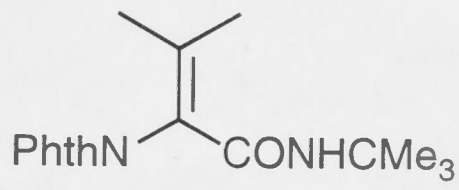


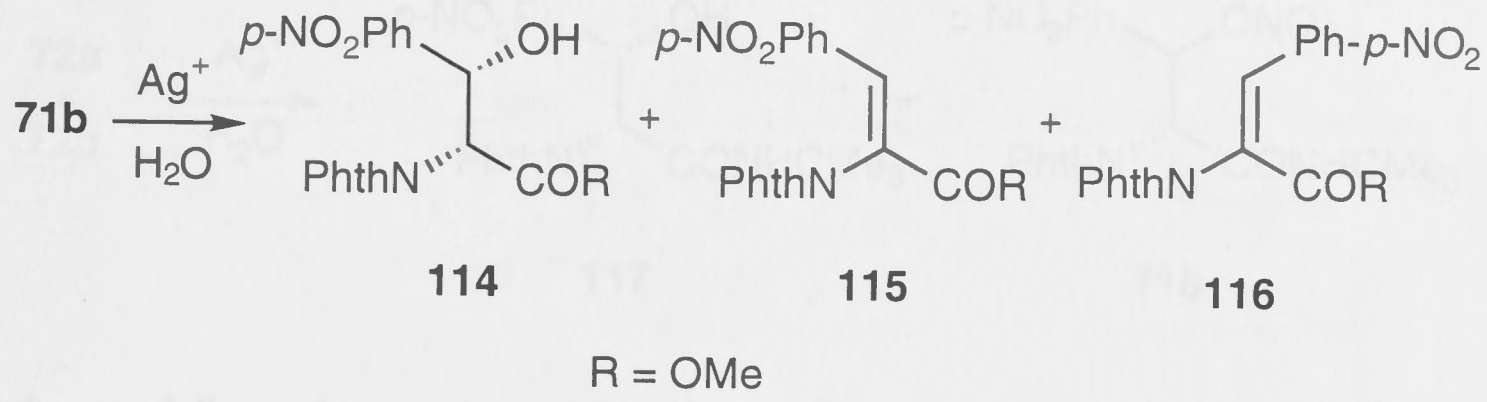
111 **112**

Scheme 2.6



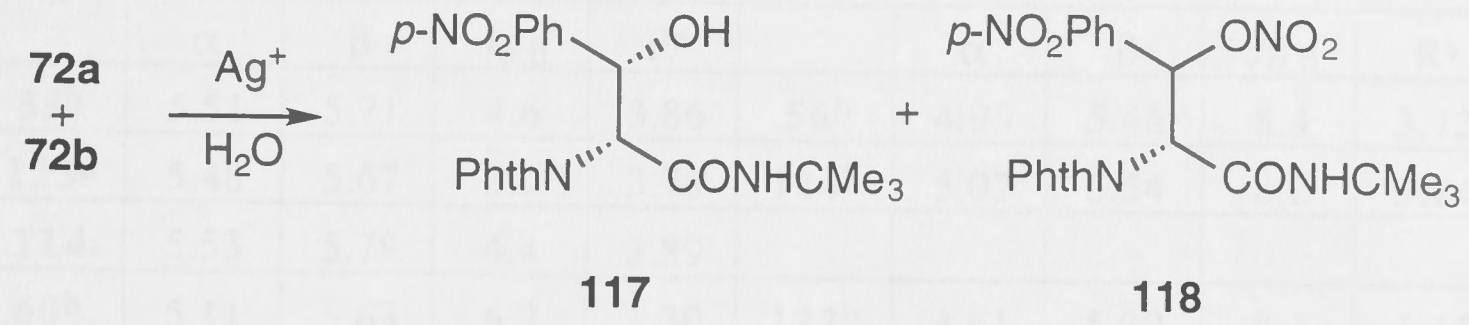
113

Hydrolysis of the bromides **71a** and **71b** was initially attempted using the same conditions as used in the hydrolysis reactions of the β-bromophenylalanine derivatives **25** and **28**, and **32a** and **32b**, however, under these conditions no reaction occurred.[59,187] The lack of reactivity of the bromides **71a** and **71b** under these conditions is attributable to the destabilising influence of the electron withdrawing nitro-substituent to limit formation of an electron deficient centre at the benzylic position. Thus, in order to facilitate the substitution process, more vigorous conditions were employed. On one occasion, treatment of the bromoester **71b** with aqueous silver nitrate at 65 °C for 48 h gave the alcohol **114** in 63% yield, with the dehydrophenylalanine derivatives **115** and **116** also being isolated as a 2:3 mixture in 25% yield (Scheme 2.7).[59,187] Repeated experiments afforded the alcohol **114** in only 10-30% yield, with the alkenes **115** and **116** making up the remainder of the products. Under similar conditions, the bromide **71a** gave only the alkene **115**, in 84% yield, and neither the alcohol **114** nor the alkene **116** was detected in the crude product.[59] Thus, reaction of the nitrophenylalanine derived bromoesters **71a** and **71b** to give mainly elimination products is in contrast to the reactions of the bromophenylalanine derivatives **25** and **28**, and **32a** and **32b**, which react exclusively by substitution.



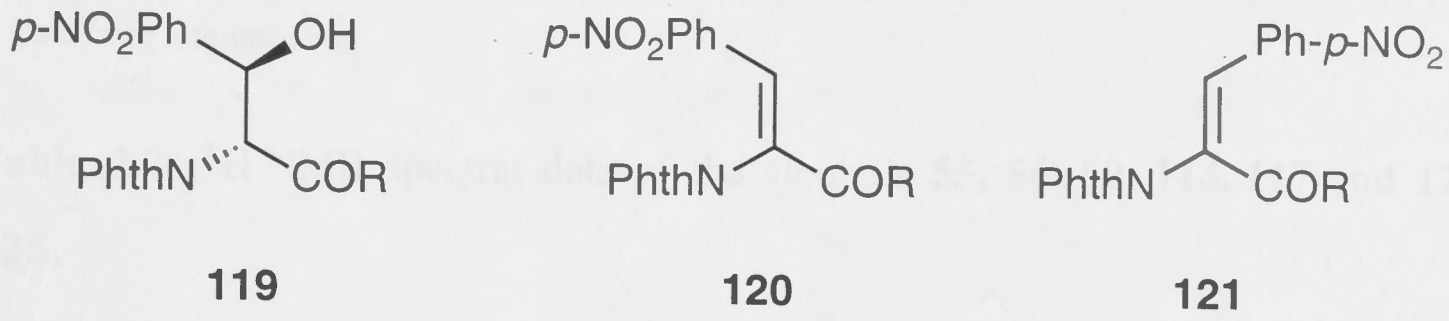
Scheme 2.7

Treatment of a 1:1 mixture of the bromoamides **72a** and **72b** with aqueous silver nitrate under similar conditions to those used in the reactions of the bromoesters **71a** and **71b** afforded a crude product which was chromatographed on silica to give the (2*R*,3*S*)-alcohol **117** in 54% yield and a second product in 19% yield, which was tentatively identified as the nitrate **118** (Scheme 2.8). Neither the (2*R*,3*R*)-alcohol **119** nor the alkenes **120** and **121** was isolated from the reaction or identified in the ^{1}H NMR spectrum of the crude material. Formation of the alcohol **117** was determined using infra-red spectroscopy, which showed a broad absorbance at 3400 cm^{-1} characteristic of an alcohol, and using ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum resonances occurred at δ 5.17 (d, *J* 4.9 Hz), 5.68 (dd, *J* 4.9 and 8.3 Hz) and 1.37 (s), corresponding to the α-, β- and *tert*-butyl protons, respectively. The assignment of peaks due to the α- and β-protons was based on comparison of the spectra of the bromides **72a** and **72b** with that of the alcohol **117**. Substitution of bromine for a hydroxyl moiety is reported to cause an upfield shift of the adjacent methine proton of 0.4 ppm.[183] Since the signals corresponding to the β-protons of the bromides **72a** and **72b** occur at δ 6.20 and 6.18, respectively, the β-hydrogen resonance of the alcohol **117** would be expected to occur at *ca.* δ 5.8. This value is in close agreement with the observed value of δ 5.68, and therefore the signal at δ 5.68 was attributed to the β-proton of the alcohol **117**.



117 **118**

Scheme 2.8



119 **120** **121**

R = $NHCMe_3$

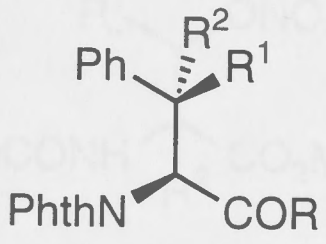
The absolute configuration at the α-carbon of the alcohols **114** and **117** is predetermined by that of the starting amino acid. (*R*)-Nitrophenylalanine was used in the initial reaction, and therefore the alcohols **114** and **117** contain the (2*R*)-stereochemistry. The relative stereochemistry of the alcohols **114** and **117** is apparent from their ^{1}H NMR spectra, from comparison with those of the β-hydroxyphenylalanine derivatives **55** and **56**, and **60** and **122** and the β-hydroxytyrosine derivatives **123**, **124** and **125** (Table 2.2).[96] The ^{1}H NMR spectrum of the hydroxyester **114** shows a much closer correlation with that of the β-hydroxyphenylalanine derivative **55** and the β-hydroxytyrosine derivative **123** than the diastereomers **56** and **124**, and indicates that the alcohol **114** has the (2*R*,3*S*)-stereochemistry. Similarly, the ^{1}H NMR spectrum of the hydroxyamide **117** shows a much closer correlation with that of the β-hydroxyphenylalanine derivative **60** and the β-hydroxytyrosine derivative **125** than with the alcohol **122**, and indicates that the alcohol **117** has the (2*R*,3*S*)-configuration.

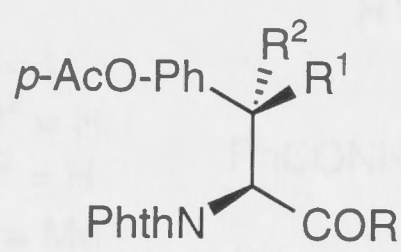
	α	β	$J_{\alpha,\beta}$	R[a]		α	β	$J_{\alpha,\beta}$	R[a]
55[b]	5.51	5.71	4.6	3.86	**56**[b]	4.95	5.46	8.4	3.72
123[b]	5.48	5.67	5.0	3.78	**124**[b]	5.02	5.54	8.2	3.74
114	5.53	5.79	4.4	3.89					
60[b]	5.11	5.63	6.2	1.30	**122**[b]	4.61	5.39	8.3	1.15
125[b]	5.08	5.63	6.3	1.31					
117	5.17	5.68	4.9	1.37					

[a] R values correspond to the signals of the carboxy protecting group.

[b] Data from reference 96.

Table 2.2. ^{1}H NMR spectral data of the alcohols **55, 56, 60, 114, 117** and **122 - 125**.



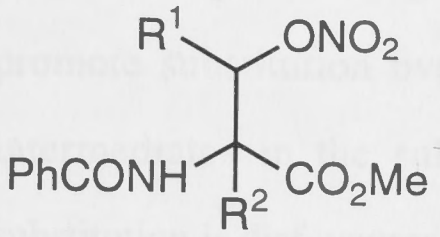


55) R = OMe, R^1 = OH, R^2 = H
56) R = OMe, R^1 = H, R^2 = OH
60) R = $NHCMe_3$, R^1 = OH, R^2 = H
122) R = $NHCMe_3$, R^1 = H, R^2 = OH

123) R = OMe, R^1 = OH, R^2 = H
124) R = OMe, R^1 = H, R^2 = OH
125) R = $NHCMe_3$, R^1 = OH, R^2 = H

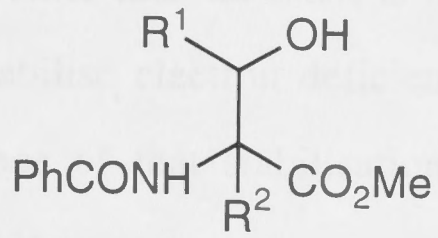
The nitrate **118** was identified by comparison of the spectral properties with those of a racemic sample. That sample was prepared from the racemates of the bromides **72a** and **72b**, by treatment with silver nitrate in aqueous acetone, as described above for the reaction of the (2*S*,3*S*)- and (2*S*,3*R*)- bromides **72a** and **72b**. The mass spectrum of the racemate of the nitrate **118** contained a peak at *m/z* 457, corresponding to the protonated molecular ion, while the ^{1}H NMR spectrum contained doublet resonances at δ 4.90 (*J*

10.7 Hz) and 7.19 (*J* 10.7 Hz), corresponding to the α- and β-protons, respectively, consistent with β-substitution. The signal corresponding to the β-proton of the nitrate **118** occurs 1.51 ppm downfield from the signal corresponding to the β-proton of the (2*R*,3*R*)-alcohol **117**. This downfield shift is similar to that observed for the signals corresponding to the protons attached to the carbons bearing the alcohol and nitrate moieties of the alcohols **127a** - **127d** and the corresponding nitrates **126a** - **126d**,[188] in which those signals are shifted downfield by *ca.* 0.9 – 1.3 ppm. On this basis, therefore, the nitrate **118** was identified. Presumably, formation of the nitrate **118** in this reaction occurs in a manner similar to that of the alcohol **117**, by nucleophilic substitution of bromine by nitrate anion. Therefore, by analogy with the alcohol **117**, the nitrate **118** is likely to contain the same relative stereochemistry as the alcohol **117**.



126

a) $R^1 = H, R^2 = H$
b) $R^1 = Me, R^2 = H$
c) $R^1 = Ph, R^2 = H$
d) $R^1 = H, R^2 = Me$



127

In order to avoid formation of the nitrate **118** in the reaction of the bromides **72a** and **72b**, it was envisaged that a silver salt containing a non-nucleophilic counterion could be used in place of silver nitrate. Silver sulfate was chosen for this purpose. Accordingly, a 1:1 mixture of the bromoamides **72a** and **72b** was treated with silver sulfate in aqueous acetone at 65 °C for 3 days. Under these conditions a crude product was obtained which was chromatographed, affording the (2*R*,3*S*)-alcohol **117** in 63% yield. Neither the (2*R*,3*R*)-alcohol **119** nor the alkenes **120** and **121** was obtained following chromatography or identified in the ^{1}H NMR spectrum of the crude product.

In order to make a comparison between the hydrolysis reactions of the nitrophenylalanine bromoesters **71a** and **71b** with those of the bromoamides **72a** and **72b**, a 1:1 mixture of the racemates of the bromoesters **71b** and **71a** was treated with silver sulfate under the same conditions as described above for the amides **72a** and **72b**. Under these conditions mainly the alkene **115** and less than 5% of either the (*E*)-isomer **116** or the racemate of the alcohol **114** were produced. The outcome of this reaction is similar to that of the reactions involving silver nitrate, which on most occasions resulted in elimination to give the alkenes **115** and **116**.

In summary, it can clearly be seen that, under comparable reaction conditions, the bromoesters **71a** and **71b** react mainly by elimination, whereas the bromoamides **72a** and **72b** react solely by substitution. Hence, in the reactions of the nitrophenylalanine derivatives **71a** and **71b** and **72a** and **72b** with aqueous silver salts, the effect of the neighbouring carboxy group, when protected as an amide rather than an ester, is to promote substitution over elimination. The amide can stabilise electron deficient intermediates in the substitution reactions. In the absence of that stabilisation, substitution is disfavoured and elimination becomes the dominant process.

As described previously, an aim of the work was to investigate the effect of the neighbouring carboxy group on the relative rates of reactions of the amino acid derivatives **18a**, **18b**, **20a**, **20b**, **33**, **71a**, **71b**, **72a**, **72b** and **73** by carrying out competitive experiments. The competitive reactions of the phenylalanine derivatives **18a**, **18b**, **20a** and **20b** and the valine derivatives **33** and **73** were carried out by treating approximately 1-2 molar equivalents of each substrate and *ca.* 0.1-0.5 molar equivalents of an internal standard with aqueous silver nitrate in acetone in the dark at room temperature for 16 h. The reactions of the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** were carried out in an oil bath at 65 °C for 16 h, in the dark using silver

sulfate. The internal standard chosen for use in these reactions was *tert*-butylbenzamide. The results obtained from a typical experiment in each case are shown in Tables 2.3, 2.4 and 2.5.

substrate	k_{rel} (Ag^+/H_2O)
18b	1.0†
18a	2.6
20b	17
20a	16

† Assigned as unity within table.

Table 2.3. Relative rates of reaction of the bromophenylalanine derivatives **18a** and **18b**, and **20a** and **20b** with aqueous silver nitrate.

substrate	k_{rel} (Ag^+/H_2O)
33	1.0†
73	6.2

† Assigned as unity within table.

Table 2.4. Relative rates of reaction of the bromovaline derivatives **33** and **73** with aqueous silver nitrate.

substrate	k_{rel} (Ag^+/H_2O)
71a	6.8
71b	1.3
72a	1.1
72b	1.0†

† Assigned as unity within table.

Table 2.5. Relative rates of reaction of the bromonitrophenylalanine derivatives **71a** and **71b**, and **72a** and **72b** with aqueous silver sulfate.

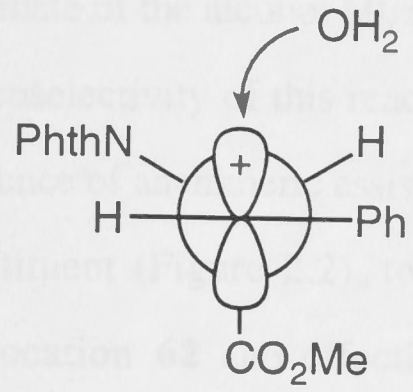
The relative reaction rates were determined using ^{1}H NMR spectroscopy, by measuring the relative rates of consumption of each substrate relative to the internal standard. Integration of peaks characteristic of the residual bromides and the internal standard, and comparison with the starting mixtures, were used to determine the percentage of each substrate remaining. From these values the ratios of the logarithms of those percentages were used to calculate the relative rates of reaction.

An indication of the reproducibility of the results was established in duplicate experiments, in which the values obtained varied by less than 20% in the reactions of the valine derivatives **33** and **73**. In the reactions of the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b**, the relative rate of reaction of the bromoamides **72a** and **72b** varied by less than 10%, while the rate of reaction of the bromoester **71a** ranged from 3.6 to 5.2 times greater than that of the isomer **71b**. The rate of reaction of the bromoester **71b** ranged from 1.2 times slower to 1.3 times faster than that of the bromoamide **72b**. In the reactions of the phenylalanine derivatives **18a**, **18b**, **20a** and **20b**, the rate of reaction of the bromoester **18a** ranged between 1.7 and 2.6 times faster than that of the bromide **18b**, while the relative rates of reaction of the bromoamides **20a** and **20b** varied by less than 20%. The rates of reaction of the bromoamides **20a** and **20b** ranged between 10-20 times faster than those of the bromoester **18b**. The variation of the rates of reaction of the amides **20a** and **20b** relative to those of the esters **18a** and **18b** can be attributed to the low extent of reaction of the bromoesters **18a** and **18b** and the high extent of reaction of the bromoamides **20a** and **20b**, due to the much greater reactivity of the amides **20a** and **20b** compared to that of the esters **18a** and **18b**. Using this method of relative reaction rate calculation, small differences in the percentage of reaction of each substrate present in the mixtures have a marked affect on the relative rates when the relative rates of reaction vary widely.

An indication of the reliability of the rates shown was determined by analysis of the mass balances of the reactions. In the reactions of the bromophenylalanine derivatives **18a**, **18b**, **20a** and **20b**, the starting materials and the racemates of the alcohols **55**, **56** and **60** comprised greater than 90% of the material present. In the reactions of the valine derivatives **33** and **73** the starting materials, the corresponding alcohols **34** and **111** and the alkenes **38**, **98** and **112** comprised approximately 90% of the material present, while in the reactions of the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b**, greater than *ca.* 70% of the ester- and amide-derived materials could be accounted for.

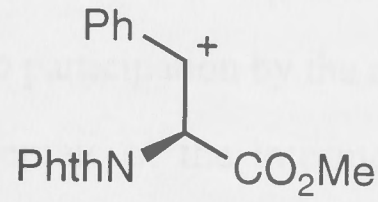
When treated under comparable conditions the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** were much less reactive than the phenylalanine derivatives **18a**, **18b**, **20a** and **20b**, however, the difference was too great to quantify accurately through competitive experiments. Presumably the lower reactivity of the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** relative to that of the corresponding phenylalanine derivatives **18a**, **18b**, **20a** and **20b** is due to the electron withdrawing effect of the nitro substituent to limit formation of electron deficient intermediates in the reactions.

In an S_N1 process, the stereochemical outcome of reaction could vary from complete retention of stereochemistry to complete inversion of configuration, whereas for an S_N2 process, only inversion of configuration results. The reaction of the bromoester **18a** to give the racemate of the alcohol **55** occurs with inversion of configuration, while there is a 2:1 preference for retention of stereochemistry in the reaction of the bromoester **18b**.[60] The logical interpretation of these results is that the bromoester **18a** reacts *via* an S_N2 process whereas an S_N1 mechanism prevails in the reaction of the bromoester **18b**. The modest stereoselectivity in the latter case can be attributed to a facial selectivity in the approach of the nucleophile to the intermediate carbocation **128** (Figure 2.1).



128

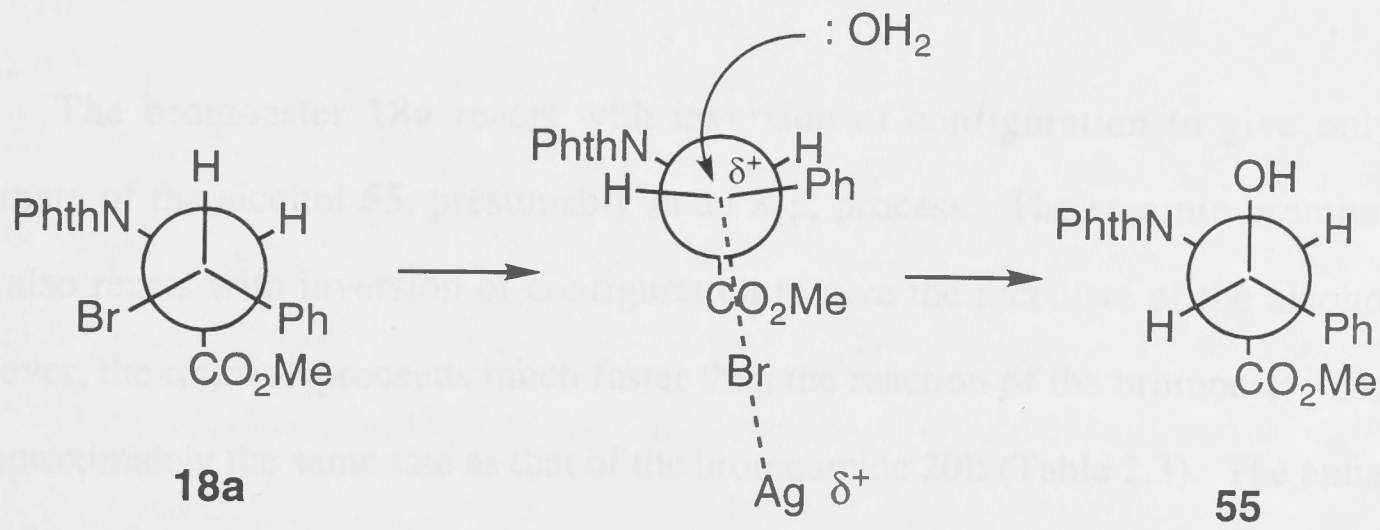
(relative stereochemistry shown only)



128

Figure 2.1. Preferred conformation of the carbocation **128**.

By comparison, for reaction of the bromide **18a**, removal of bromine to give the preferred conformation of the carbocation **128** occurs less readily than in the reaction of the bromoester **18b** since rotation about the C2-C3 bond is required, and this would cause steric crowding between the ester moiety and the dissociating bromine. In contrast, attack of water from behind the breaking carbon-bromine bond is not hindered. Hence it is presumed that the reaction of the bromide **18a** occurs *via* an S_N2 type mechanism, where the silver ion coordinates to the bromine and assists in breaking the carbon-bromine bond as water attacks from the opposite face, to give the racemate of the alcohol **55** (Scheme 2.9).



18a **55**

Scheme 2.9 (relative stereochemistry shown only)

The racemic bromoamide **20b** reacts with retention of configuration to give the racemate of the alcohol **60**, presumably in an S_N1 process. The faster rate and enhanced stereoselectivity of this reaction compared to that of the bromoester **18b** is convincing evidence of anchimeric assistance and 1,4-neighbouring group participation by the amido substituent (Figure 2.2), to facilitate formation of the racemate of the intermediate carbocation **62** and effectively block one face of that species to reaction with the incoming nucleophile. Presumably, direct interaction of the amido substituent with the benzylic carbocation locks the conformation of the intermediate **62** such that the incoming nucleophile can only approach from the face of the intermediate species **62** opposite the amido moiety (Figure 2.2) to afford only the racemate of the alcohol **60**.

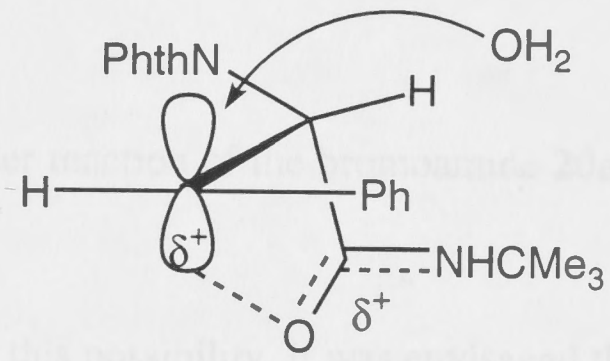
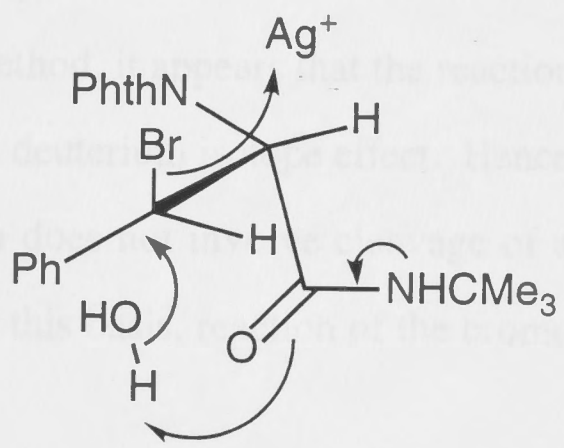


Figure 2.2. Stabilisation of the carbocation **62** by the amido substituent.

The bromoester **18a** reacts with inversion of configuration to give only the racemate of the alcohol **55**, presumably in an S_N2 process. The racemic bromoamide **20a** also reacts with inversion of configuration to give the racemate of the alcohol **60**, however, the reaction proceeds much faster than the reaction of the bromoester **18a** and at approximately the same rate as that of the bromoamide **20b** (Table 2.3). The enhanced rate of reaction of the bromoamide **20a** compared to that of the corresponding bromoester **18a** is inconsistent with simple S_N2 displacement of bromine, as the amide **20a** would

then be expected to react slower than the ester **18a** due to hindrance to approach of the incoming nucleophile by the bulky amido substituent. One interpretation of this result is that the amido substituent, being approximately 10^6 times more basic than the ester moiety,[115] facilitates the second order reaction by acting as a base to promote the nucleophilicity of water (Figure 2.3).



(relative stereochemistry shown only)

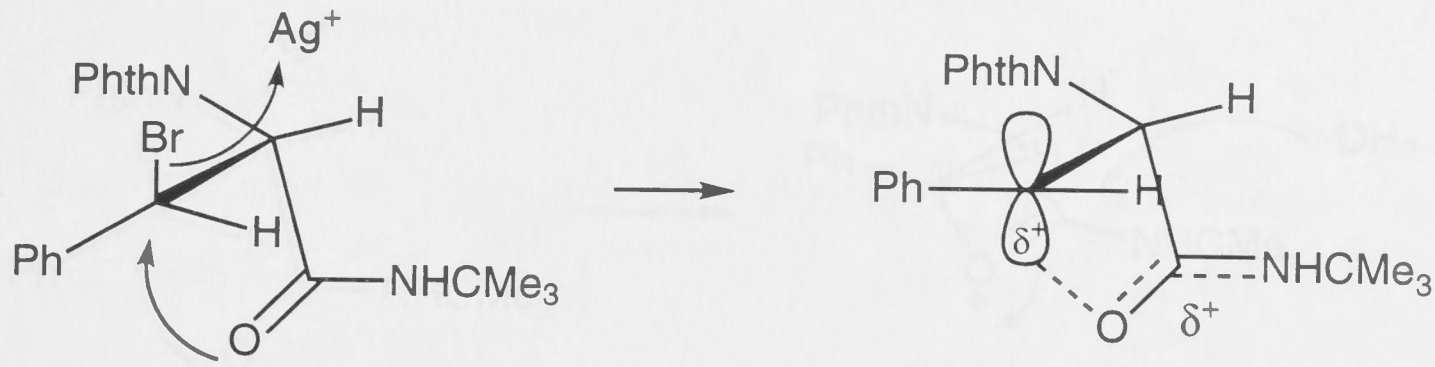
Figure 2.3. Second order reaction of the bromoamide **20a**.

In order to check this possibility, it was envisaged that a competitive reaction of the bromoamides **20a** and **20b** using deuterated water could be used. The second order reaction of the bromoamide **20a** with aqueous silver nitrate involves cleavage of a hydrogen–oxygen bond of water (Figure 2.3). In comparison, the first order reaction of the bromoamide **20b** does not involve cleavage of a hydrogen–oxygen bond in the transition state of the reaction. Therefore, only the rate of reaction of the bromide **20a** using deuterium oxide is likely to be affected by a deuterium isotope effect associated with cleavage of the deuterium–oxygen bond, and hence a slower reaction rate than that of the bromide **20b** in a competitive experiment under these conditions would be expected. Therefore, this experiment could be used to distinguish between a first and second order process in the reaction of the bromoamide **20a**. Hence, an approximately 1:1 mixture of the bromoamides **20a** and **20b** was treated with silver nitrate in deuterium

oxide and acetone in a competitive experiment, using the procedure described above, and the relative rates of reaction were determined.

Using these conditions, the rate of reaction of the bromoamide **20b** was determined to be 1.1 times faster than that of the bromoamide **20a**. Differences in the solvation of both the silver ion and the substrates and intermediates by deuterium oxide compared to water could affect the reaction. Taking into consideration these factors as well as the experimental error associated with determination of the relative reaction rates using this method, it appears that the reactions of the bromoamides **20a** and **20b** are not affected by a deuterium isotope effect. Hence, this result suggests that the reaction of the bromide **20a** does not involve cleavage of a deuterium–oxygen bond in the transition state, and on this basis, reaction of the bromoamide **20a** *via* a second order process was discounted.

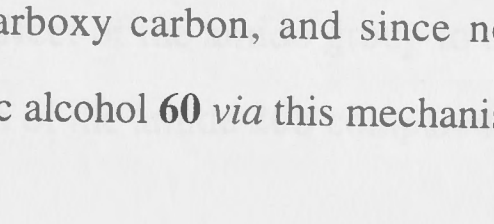
An alternative explanation to account for the enhanced rate of reaction of the bromoamide **20a** compared to that of the bromoester **18a** involves facilitation of a first order process by the amido substituent of the amide **20a**. In the orientation of the bromoamide **20a** required for neighbouring group participation by the amido substituent, carbocation formation occurs such that the bulky phenyl substituent is in close proximity to the phthalimido moiety (Scheme 2.10), which is unfavourable due to steric crowding. Relief of these unfavourable steric interactions occurs through rotation about the C2-C3 bond of the racemate of the carbocation **62** in the initially formed conformation, which is shown in Scheme 2.10, to give the most stable orientation (Figure 2.2). Approach of the nucleophile from the face opposite to the amido moiety of the carbocation **62** in the conformation shown in Scheme 2.10 would afford the racemate of the alcohol **122**, with retention of configuration. Presumably, since none of the alcohol **122** is produced in the reaction, rotation about the C2-C3 bond occurs to give the racemate of the carbocation **62** in its preferred orientation (Figure 2.2) much faster than reaction in its initial orientation (shown in Scheme 2.10) with water.



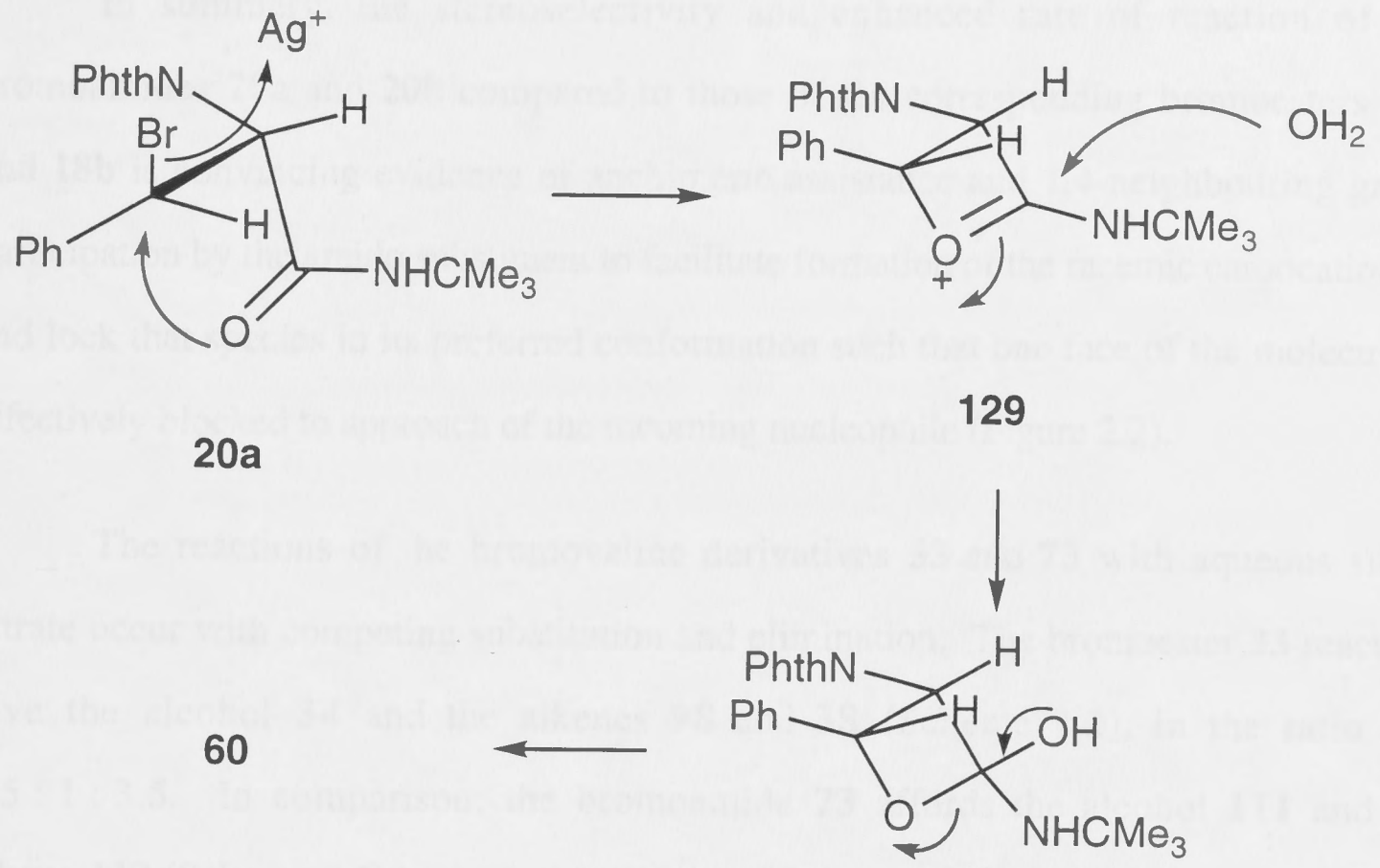
20a **62**

(relative stereochemistry shown only)

Scheme 2.10



Another mechanism considered which could account for the stereochemical outcome of the reaction of the bromoamide **20a** and the enhanced rate of reaction compared to that of the corresponding ester **18a** involved displacement of bromine by the amido moiety to give the formally bonded species **129** similar to the stabilised intermediate **62**, followed by nucleophilic attack by water at the carboxy carbon and ring opening (Scheme 2.11). This mechanism involving 1,4-neighbouring group participation and anchimeric assistance by the amido group could account for the faster rate of reaction of the amide **20a** compared to that of the ester **18a**, however, it does not account for the high stereoselectivity of reaction. Nucleophilic attack at the β-carbon of the intermediate **129** from the face opposite to the amido moiety to give the alcohol **122** could occur in addition to reaction at the carboxy carbon, and since none of the alcohol **122** was produced, formation of racemic alcohol **60** *via* this mechanism is considered unlikely.



Scheme 2.11

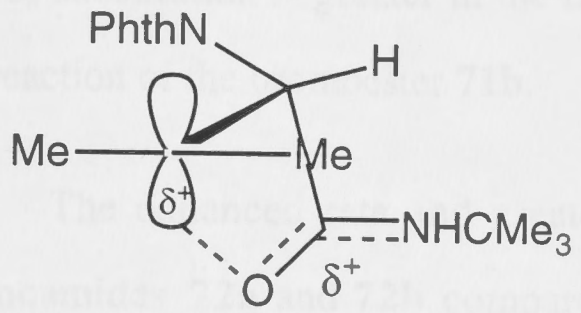
Several other explanations for the results obtained in the hydrolysis reactions of the phenylalanine derivatives **18a**, **18b**, **20a** and **20b** were considered, however, these do not account for the kinetic effects and the stereochemical outcome of the reactions. One possible explanation which could account for the high stereoselectivity of reaction of the phenylalanine derivative **20b** compared to that from reaction of the corresponding ester **18b**, is that the greater bulk of the *tert*-butyl amide group results in a greater conformational preference of the intermediate racemic carbocation **62** than for the racemic carbocation **128**, such that approach of the nucleophile only occurs from the least hindered face of the molecule, opposite to the carboxy group. However, this explanation was discounted since it has been shown[96] that the stereoselectivity of formation of the alcohols **58** and **59** from reaction of the *tert*-butyl esters **57a** and **57b** (Scheme 15) was only 8:1 despite the very similar size of the *tert*-butyl ester and *tert*-butyl amide moieties. Hence, this indicates that the effect of the amido group to dramatically increase the rate and stereoselectivity of reaction of the amide **20b** compared to the ester **18b** is not due to steric influences.

In summary, the stereoselectivity and enhanced rate of reaction of the bromoamides **20a** and **20b** compared to those of the corresponding bromoesters **18a** and **18b** is convincing evidence of anchimeric assistance and 1,4-neighbouring group participation by the amido substituent to facilitate formation of the racemic carbocation **62** and lock that species in its preferred conformation such that one face of the molecule is effectively blocked to approach of the incoming nucleophile (Figure 2.2).

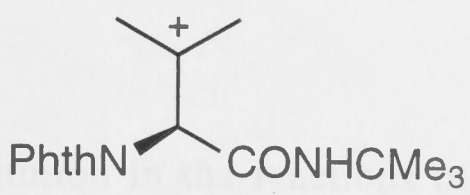
The reactions of the bromovaline derivatives **33** and **73** with aqueous silver nitrate occur with competing substitution and elimination. The bromoester **33** reacts to give the alcohol **34** and the alkenes **98** and **38** (Scheme 1.2), in the ratio *ca.* 3.5 : 1 : 3.5. In comparison, the bromoamide **73** affords the alcohol **111** and the alkene **112** (Scheme 2.6) in the ratio *ca.* 2 : 1 and the reaction occurs approximately six times faster than the corresponding reaction of the bromoester **33** (Table 2.4). That is, not only does substitution occur to a greater extent in the reaction of the bromoamide **73** than in the reaction of the bromoester **33**, the reaction also proceeds much faster. Therefore, the effect of the carboxy group, when protected as an amide rather than an ester, is to enhance the substitution process, to the extent that substitution is favoured over elimination.

In the absence of stabilisation by the amido group, elimination is the dominant process. Through stabilisation of the carbocation intermediate **130** by the amido group in the reaction of the valinamide **73**, substitution competes more effectively with elimination, to the extent that substitution is favoured over elimination. Presumably, the substitution process is enhanced by the amido substituent in the reaction of the bromovaline derivative **73** in an analogous manner to that in the reactions of the bromophenylalanine derivatives **20a** and **20b**, through direct interaction and stabilisation of the carbocation intermediate **130** (Figure 2.4). Hence, the reaction of the

bromide **73**, as a consequence of neighbouring group participation by the amido substituent to stabilise the intermediate carbocation **130**, provides an efficient route to the alcohol **111**, a derivative of the naturally occurring β-hydroxyvaline **35**.



130



130

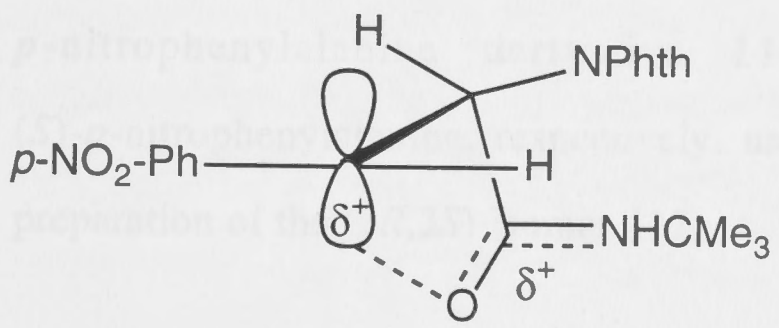
Figure 2.4. Stabilisation of the carbocation **130** by the amido moiety.

The neighbouring group effect of the aminocarbonyl substituent to promote substitution over elimination is also seen in the reactions of the nitrophenylalanine derivatives **71a** and **71b**, and **72a** and **72b** with silver sulfate. By comparison with the bromophenylalanine derivatives **18a** and **18b**, **20a** and **20b** which react solely by substitution, the bromoesters **71a** and **71b** react mainly by elimination. Therefore, the effect of the nitro substituent in the hydrolysis reactions of the esters **71a** and **71b** is to destabilise electron deficient intermediates to the extent that elimination is favoured over substitution. In the reactions of the amides **72a** and **72b**, however, the dominant reaction is substitution. Hence, the effect of the amido group in these reactions is to diminish the destabilising influence of the nitro-aromatic substituent such that substitution becomes the dominant process.

In the competitive experiments involving the bromides **71a**, **71b**, **72a** and **72b**, the bromoesters **71a** and **71b** reacted to give less than 5% of the alcohol **114**, whereas

the amides **72a** and **72b** reacted by substitution and at a very similar rate to that of the bromoester **71b**. That is, substitution occurs to a much greater extent in the reactions of the bromoamides **72a** and **72b** and proceeds much faster than in the reactions of the bromoesters **71a** and **71b**. This is not merely a steric effect of the bulky aminocarbonyl substituent to retard elimination due to crowding with the phthalimido group, since the rate of substitution is greater in the reactions of the bromoamides **72a** and **72b** than in the reaction of the bromoester **71b**.

The enhanced rate and greater extent of substitution in the reactions of the bromoamides **72a** and **72b** compared to the reactions of the esters **71a** and **71b** is consistent with 1,4-neighbouring group participation by the amido substituent to stabilise electron deficient intermediates of reaction. Presumably the origin of the effects seen in the reactions of the nitrophenylalanine derivatives **72a** and **72b** is analogous to that described above for the reactions of the corresponding phenylalanine derivatives **20a** and **20b**. The bromoamide **72a** reacts with inversion of configuration to give the alcohol **117**, whereas the bromide **72b** reacts with retention of configuration to give the same. By analogy with the reactions of the bromoamides **20a** and **20b**, the bromides **72a** and **72b** react *via* S_N1 processes facilitated by direct 1,4-participation by the amido substituent with the carbocation centre of the intermediate **131** (Figure 2.5).



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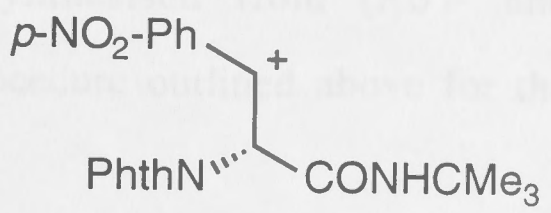
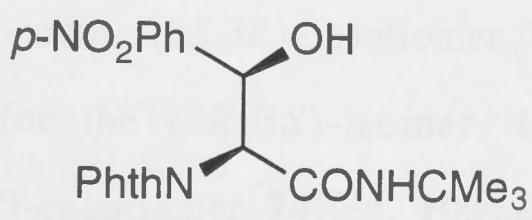


131

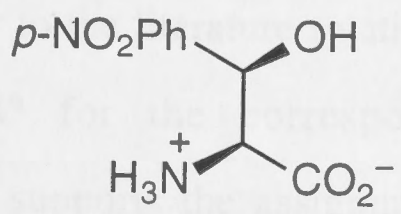
Figure 2.5. Stabilisation of the carbocation **131** by the amido group.

In summary, the effect of the amido substituent in the reactions of the phenylalanine derivatives **20a** and **20b** is to enhance the rate and stereoselectivity of substitution compared to the reactions of the corresponding esters **18a** and **18b**, through direct interaction with the electron deficient benzylic carbocation **62**. In a similar manner, the amido substituent facilitates reaction of the valinamide **73** through 1,4-neighbouring group participation by interacting directly with the electron deficient carbocation centre of the intermediate **130**, such that substitution is enhanced to the extent that substitution is favoured over elimination. The effect of the amido substituent to promote substitution over elimination is also seen in the reactions of the nitrophenylalanine derivatives **72a** and **72b**. Whereas elimination is the dominant process in the reactions of the esters **71a** and **71b**, the amides **72a** and **72b** react solely by substitution, as a consequence of direct 1,4-neighbouring group participation by the amido substituent, through interaction with the electron deficient carbocation **131**.

As mentioned previously, it was envisaged that the effect of the protected carboxy group to influence the stereoselectivity of reactions of the bromophenylalanine derivatives **25**, **28**, **32a** and **32b** could be exploited in the stereocontrolled synthesis of the chloramphenicol precursor **74**, by hydrolysis of the (2*S*,3*R*)-alcohol **132**. Previously the racemate of the alcohol **74** has been elaborated to chloramphenicol **54**,[124] and the process would therefore provide a stereocontrolled route to the natural product **54**. Hence, the racemate and the (2*S*,3*R*)-enantiomer **132** of the β-hydroxy-*p*-nitrophenylalanine derivative **117** were synthesised from (*RS*)- and (*S*)-*p*-nitrophenylalanine, respectively, using the procedure outlined above for the preparation of the (2*R*,3*S*)-isomer **117**.

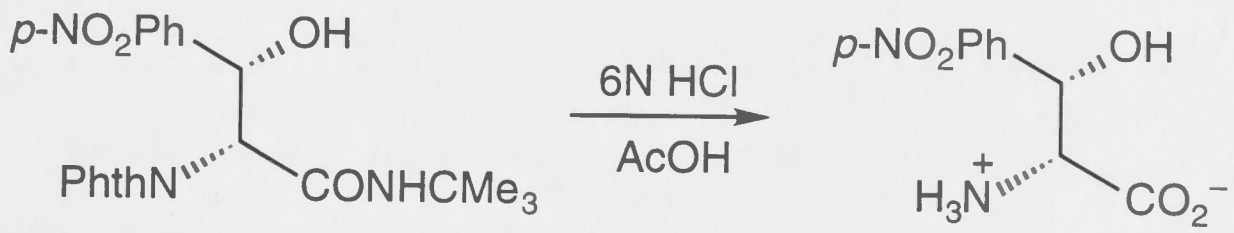


132



74

In order to obtain the free amino acid **133**, the (2*R*,3*S*)-alcohol **117** was deprotected using standard conditions by treatment with a mixture of 6N hydrochloric acid and acetic acid, and the (2*R*,3*S*)-amino acid **133** was isolated in 69% yield. The procedure used to prepare the (2*R*,3*S*)-amino acid **133** from the (2*R*,3*S*)-alcohol **117** was repeated using the racemate and the (2*S*,3*R*)-enantiomer **132** of the (2*R*,3*S*)-alcohol **117**, from which the (2*S*,3*R*)-enantiomer **74** and the racemate of the amino acid **74** were obtained.



117 **133**

Scheme 2.12

The relative stereochemistry of the amino acids **74** and **133** was determined using ^{1}H NMR spectroscopy, which showed doublets at δ 5.77 (*J* 3.9 Hz) and 4.70 (*J* 3.9 Hz) corresponding to the β- and α-protons, respectively, by comparison with literature values.[189] The absolute stereochemistry and optical purity was determined from the specific rotations of the (2*S*,3*R*)-enantiomer **74** and the (2*R*,3*S*)-isomer **133**. The values obtained were +35.3° for the (2*R*,3*S*)-isomer **133** and –36.4° for the corresponding (2*S*,3*R*)-enantiomer **74**, which are similar to the literature rotations of +27° for the (2*R*,3*S*)-isomer **133**[189] and –33.8° for the corresponding (2*S*,3*R*)-enantiomer **74**.[124] Hence, this result further supports the assignment of stereochemistry of the alcohol **117**, since it is the alcohol **117** which affords the free

amino acid **133**. Now stereocontrolled access to the (2*S*,3*R*)-amino acid **74**, as a consequence of neighbouring group participation by an aminocarbonyl substituent to facilitate substitution over elimination and control the stereochemistry of the former, offers a more direct route for synthesis of the antibiotic **54**.

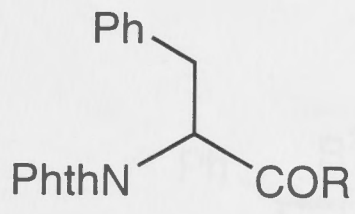
RESULTS AND DISCUSSION: CHAPTER 3

Anchimeric Assistance in Hydrogen Atom Transfer Reactions on the Side Chains of Amino Acid Derivatives

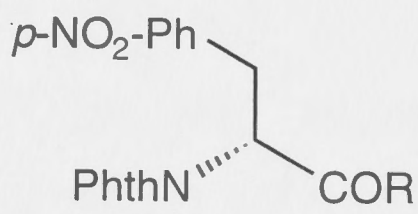
Neighbouring group participation in ionic reactions is very common, although the incidence of 1,4-participation is limited. In the previous Chapter, the hydrolysis reactions of the bromophenylalanine derivatives **18a**, **18b**, **20a** and **20b**, the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** and the valine derivatives **33** and **73** were examined. The rate and in some cases the stereoselectivity of substitution were dramatically affected by the nature of the protected carboxy group, which was attributed to 1,4-neighbouring group participation by the carboxy group, when protected as an amide rather than as an ester, through direct interaction with electron deficient carbocation intermediates. In contrast to their ionic counterparts, the incidence of neighbouring group participation in radical reactions is rare, particularly examples of 1,4-participation, which appear to be extremely uncommon. The effect of the carboxy substituent, when protected as an amide, to exert 1,4-neighbouring group participation in the hydrolysis reactions of the brominated amino acid derivatives **20a**, **20b**, **72a**, **72b** and **73** prompted the investigation into the possibility of 1,4-neighbouring group participation in side chain radical reactions of amino acid derivatives, which will be the topic of discussion in this Chapter.

The phenylalanine derivatives **17** and **19** and the nitrophenylalanine derivatives **78a** and **78b**, which were prepared in the previous Chapter, and the tyrosine derivatives **79a** and **79b**[96] were thought to be suitable substrates to investigate the possibility of neighbouring group participation in their side chain bromination reactions. These reactions may be assumed to proceed *via* hydrogen abstraction by bromine atom to give the corresponding intermediate radicals **21**, **22**, **134a**, **134b**, **135a** and **135b**, which are similar to the carbocation intermediates **62** and **128** of the hydrolysis reactions of the

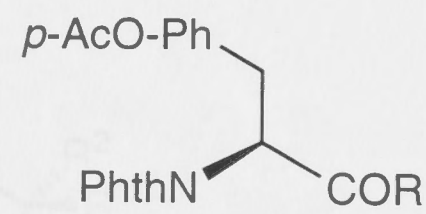
bromides **25**, **32a** and **32b**, since the radicals **21**, **22**, **134a**, **134b**, **135a** and **135b** are electron deficient and sp^2-hybridised at the β-carbon. By analogy with the hydrolysis reactions described in the previous Chapter, it was thought that the bromination reactions could involve interaction between the carboxy group and the radical centre, and hence they provide the opportunity to probe for neighbouring group participation in the side chain radical bromination processes.



17) R = OMe
19) R = $NHCMe_3$

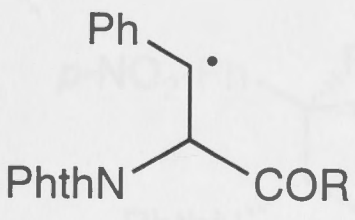


78

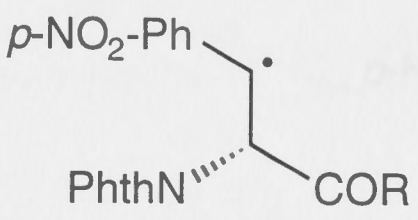


79

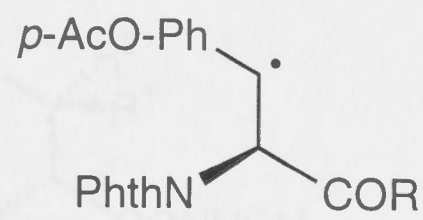
a) R = OMe
b) R = $NHCMe_3$



21) R = OMe
22) R = $NHCMe_3$



134

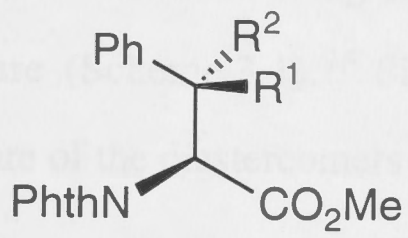


135

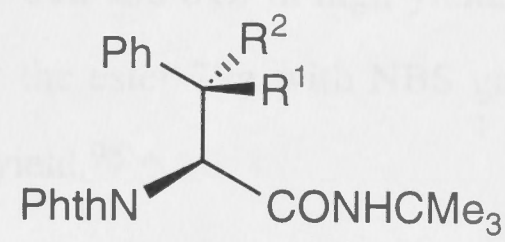
a) R = OMe
b) R = $NHCMe_3$

In addition to the bromination reactions mentioned above, it was anticipated that the reverse transformations of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** to the corresponding reduced materials **17**, **19**, **78a**, **78b**, **79a** and **79b** using triphenyltin hydride could be used to probe for neighbouring group participation in side chain radical reactions, since these processes are also likely to proceed *via* the radical intermediates **21**, **22**, **134a**, **134b**, **135a** and **135b**.

Furthermore, as a result of the contrasting polar nature of the processes involving NBS and triphenyltin hydride, an insight into the nature of the reaction transition states could also be gleaned. Therefore, an aim of the work described in this Chapter was to investigate the possibility of neighbouring group participation in side chain radical bromination reactions of the amino acid derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** with NBS and in the reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** with triphenyltin hydride.

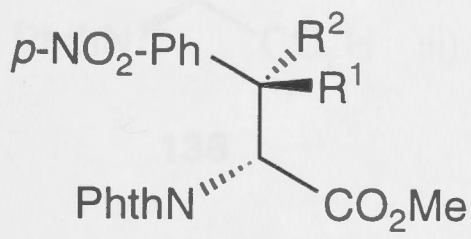


18



20

(stereochemical descriptors show relative stereochemistry only)



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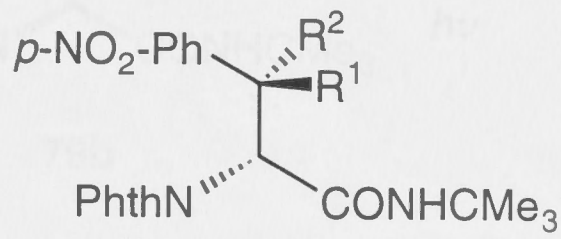
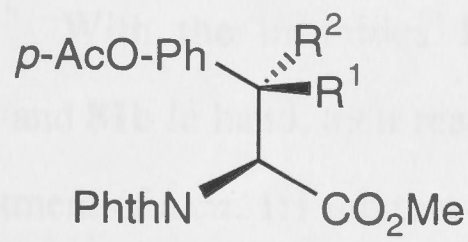
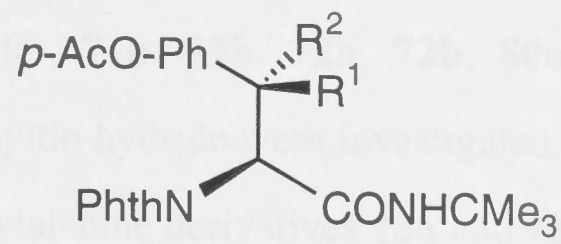


72



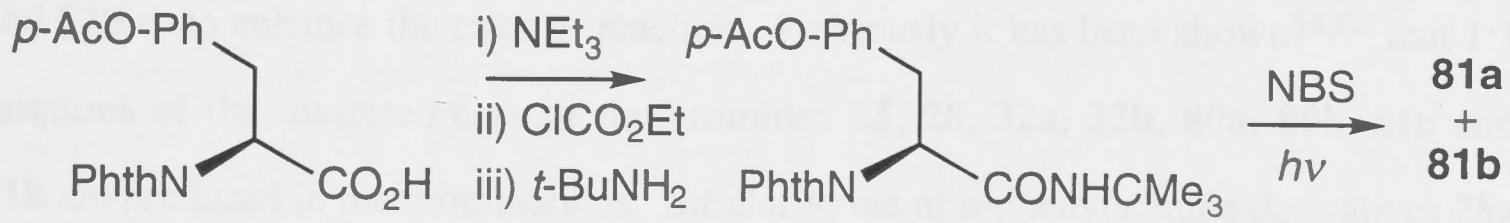
80



81

a) R^1 = H, R^2 = Br
b) R^1 = Br, R^2 = H

The phenylalanine derivatives **17**, **18a**, **18b**, **19**, **20a** and **20b** and the nitrophenylalanine derivatives **71a**, **71b**, **72a**, **72b**, **78a** and **78b** used in this investigation were prepared as described in the previous Chapter. The *N*-phthaloyltyrosine derivative **136** and the corresponding ester **79a** were available for use.[59,96] The bromoesters **80a** and **80b**, the amide **79b** and the bromoamides **81a** and **81b** were prepared as described previously.[59] Accordingly, treatment of *O*-acetyl-*N*-phthaloyltyrosine **136** with triethylamine, ethyl chloroformate and then *tert*-butylamine afforded the tyrosinamide **79b** in 75% yield. Bromination of the amide **79b** under the standard conditions using NBS gave the isomers **81a** and **81b** in high yield, as a 1:1 mixture (Scheme 3.1).[96] Similarly, treatment of the ester **79a** with NBS gave a 1:1 mixture of the diastereomers **80a** and **80b** in high yield.[96]



136 **79b**

Scheme 3.1

With the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** in hand, their reactions with triphenyltin hydride were investigated. Thus, treatment of a *ca.* 1:1 mixture of the bromophenylalanine derivatives **18a** and **18b** with triphenyltin hydride in benzene under nitrogen, with irradiation from a 300 W sunlamp, afforded the corresponding phenylalanine ester derivative **17** in good yield. Under identical conditions, a mixture of the bromoamides **20a** and **20b** reacted with triphenyltin hydride to give the corresponding phenylalanine derivative **19**, also in good yield. Under

similar conditions the nitrophenylalanine bromoesters **71a** and **71b** reacted with triphenyltin hydride to give the ester **78a**, while the bromoamides **72a** and **72b** reacted to give the amide **78b**. However, analysis of the crude products from these reactions using ^{1}H NMR spectroscopy showed that some decomposition had occurred. Treatment of the bromotyrosinamides **81a** and **81b** and the tyrosine bromoesters **80a** and **80b** with triphenyltin hydride afforded the reduced analogues **79b** and **79a**, respectively. As with the reactions of the nitrophenylalanine derivatives **71a** and **71b**, and **72a** and **72b**, analysis of the crude products of these reactions using ^{1}H NMR spectroscopy showed that some decomposition had occurred under the reaction conditions.

Participation by the neighbouring carboxy protecting group in the reactions of the phenylalanine, tyrosine and nitrophenylalanine derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** with NBS has the potential to result in stereoselective formation of the corresponding bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** or to enhance the rates of reaction. Previously it has been shown[54,60] that 1:1 mixtures of the diastereomers of the bromides **25**, **28**, **32a**, **32b**, **80a**, **80b**, **81a** and **81b** are produced in the brominations. Similarly, the nitrophenylalanine derivatives **78a** and **78b** reacted with NBS to give 1:1 mixtures of the diastereomers of the bromides **71a** and **71b**, and **72a** and **72b**, respectively. The lack of stereoselectivity in these reactions indicates that the bromination reactions are not affected by steric constraints imposed by the bulky phthaloyl moiety, carboxy protecting group and phenyl substituent in the delivery of bromine to the (2*S*)-enantiomers of the intermediate benzylic radicals, and can be attributed to the low energy of activation of such halogen atom transfer processes.[25]

In order to investigate the effect of the neighbouring carboxy group on the rates of the radical brominations, various mixtures of the amino acid derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** were treated with approximately one molar equivalent of NBS in competitive experiments. In these reactions, solutions of the substrates and *tert*-butyl

benzamide, an internal standard, in carbon tetrachloride were heated at reflux under an atmosphere of nitrogen, with initiation from irradiation by a 300 W sunlamp, and the crude mixtures were analysed using ^{1}H NMR spectroscopy.

The relative rates of reaction were determined using ^{1}H NMR spectroscopy in a manner identical to that described in Chapter 2 of the Results and Discussion of this thesis for the reactions of the bromides **18a**, **18b**, **20a**, **20b**, **33**, **71a**, **71b**, **72a**, **72b** and **73** with silver salts, by measuring the relative rates of consumption of the substrates **17**, **19**, **78a**, **78b**, **79a** and **79b** relative to the internal standard. In duplicate experiments the relative rates determined varied by less than 20%. An indication of the reliability of the rates shown (Table 3.1) was determined by analysis of the mass balance of the starting materials and products in the reactions. In most cases, the starting materials and the product comprised greater than 80% of the material present and the extent of reaction was between 20-80%. The results of these experiments are summarised in Table 3.1.

substrate	k_{rel} (NBS)
17	8
19	40
79a	9
79b	34
78a	1†
78b	5

† Assigned as unity within column.

Table 3.1. Relative rates of reactions of the amino acid derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** with NBS.

As described above, another aim of the work was to investigate the possibility of neighbouring group participation in the reduction reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** using triphenyltin hydride, by determining the effect of the carboxy substituent on the relative rates of reaction. Hence, the relative rates of reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** were determined in competitive experiments. In these competitive experiments, various mixtures of approximately equimolar amounts of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** and *tert*-butylbenzamide in benzene were treated with less than one molar equivalent of triphenyltin hydride with initiation from irradiation by a 300 W sunlamp. The relative rates were determined from the ratios of products in the reaction mixtures, which were corrected to allow for the initial ratios of substrates in the mixtures, and confirmed through duplicate experiments. The relative rates determined from the duplicate experiments using this method varied by less than 20% in most cases, except in reactions involving the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** which were complicated by competing decomposition. The results of these experiments are summarised in Table 3.2.

Compounds	$k_{rel}(Ph_3SnH)$
18a and **18b**	1†
20a and **20b**	1
80a and **80b**	1.2
81a and **81b**	1.4
71a and **71b**	4
72a and **72b**	4

† Assigned as unity within table.

Table 3.2. Relative rates of reaction of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** with triphenyltin hydride, as determined from product ratios.

The relative rates of reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** could also be determined by measuring their relative rates of consumption from mixtures, relative to the internal standard, as described above for the reactions involving NBS. However, calculation of the relative rates of reaction using this method was complicated in some cases due to decomposition under the reaction conditions, as determined by analysis of the material balance of the reactions. In most cases, the brominated substrate and the reduced product comprised greater than *ca.* 80% of the material present. In the reactions involving the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b**, however, a significant amount of the material could not be accounted for, presumably due to decomposition under the reaction conditions. For example, in several of the experiments involving the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b**, these bromides and the corresponding reduced materials **78a** and **78b** comprised less than 50% of the material identified in the crude product. In addition, decomposition of these materials also affected the reduction of other substrates. Hence, determination of the relative rates using this method was found to be unreliable. The results of these experiments are summarised in Table 3.3. The data used to compile this table were obtained from single experiments in which the mass balance was considered reliable (generally greater than 80% of the material accounted for) and where most of the bromides consumed afforded reduced materials.

In the reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** with triphenyltin hydride, there is a possibility of stereoselectivity. To examine this possibility in the reactions of the bromides **18a** and **18b**, a *ca.* 1:1 mixture of the bromophenylalanine derivatives **18a** and **18b** was treated with triphenyltin hydride as described above for the competitive experiments. Under these conditions, the stereoselectivity was less than 1.1. In a similar manner, reactions of the bromoamides **20a** and **20b** were examined for the possibility of stereoselectivity, and in this case, no stereoselectivity was observed.

substrate	k_{rel}
18b	1†
20b	1
80b	1.1
81b	1.3
71a	6
72a	6

† Assigned as unity within table.

Table 3.3. Relative rates of reactions of the bromides **18b**, **20b**, **71a**, **72a**, **80b** and **81b**, based on their rates of consumption from mixtures.

The stereoselectivity of reaction of the bromides **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** was determined from the competitive reactions between the substrates. In the reactions of the nitrophenylalanine derivatives **71a** and **71b**, the diastereomer **71a** reacted approximately 1.6 times faster than the bromide **71b**, however, the ratio of the reduced material **78a** to consumed bromides **71a** and **71b** was low, and approximately 50% of the material could not be accounted for, presumably due to decomposition. Consequently, it is not clear whether the observed diastereoselectivity of 1.6:1 is real or mainly due to decomposition. The bromoamide **72a** reacted less than 1.4 times faster than the diastereomer **72b**. As with the reaction of the esters **71a** and **71b**, the ratio of the reduced material **78b** to consumed bromides **72a** and **72b** was low and approximately 50% of the material could not be accounted for in these reactions. Hence, this selectivity could also be due mainly to decomposition.

The bromotyrosine derivatives **80a** and **80b** reacted with a stereoselectivity which varied between 1:1.1 and 1:1.5, while the bromoamides **81a** and **81b** reacted with a stereoselectivity of less than 1.4:1. In the reactions of the esters **80a** and **80b**, the ratio of reduced material **79a** to consumed bromides **80a** and **80b** was low and approximately

20% of the material could not be accounted for. Hence, the stereoselectivity of less than 1:1.5 could be a result of selective decomposition of the (2*R*,3*S*)-isomer **80a**.

In summary, the reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** with triphenyltin hydride proceed with little stereoselectivity, most of which could be due to selective decomposition of one isomer under the reaction conditions. The relative rates of reactions were determined by measuring the relative rates of production of the reduced materials, from their ratio in the crude mixtures, or from the rates of consumption of bromides from the mixtures. As a result of decomposition during some reactions, the relative rates determined from the product ratios are likely to be the most reliable.

In the competitive experiments described above involving NBS, the phenylalanine derivatives **17** and **19** and the tyrosine derivatives **79a** and **79b** reacted much faster than the corresponding nitro-substituted analogues **78a** and **78b**, respectively (Table 3.1). For example, the phenylalanine derivatives **17** and **19** reacted approximately eight times faster than the corresponding nitro-substituted analogues **78a** and **78b**. From this data, using the Hammett equation and a $\sigma_{p(NO_2)^+}$ constant of 0.79,[190] a rho (ρ) value of *ca.* −1.1 was obtained. The effect of the aromatic ring substituents in these reactions is similar to that previously reported for radical bromination of series of substituted toluene derivatives,[27,28,191] in which a ρ value of −1.4 was obtained and is consistent with the transition state proposed for radical bromination, in which hydrogen transfer to electrophilic bromine atom occurs with the development of an electron deficient centre at the site of hydrogen abstraction (Figure 1).[27,28] Thus, as a result of positive charge development in the transition state, radical formation adjacent to the electron deficient nitro substituted aromatic moiety is disfavoured, such that the nitrophenylalanine derivatives **78a** and **78b** react slower than the corresponding phenylalanine and tyrosine derivatives **17**, **19**, **79a** and **79b**.

In the processes involving triphenyltin hydride, the effect of the nitro substituent is the reverse of that seen in the reactions with NBS, with the nitro-substituted compounds **71a** and **71b**, and **72a** and **72b** reacting faster than the corresponding phenylalanine and tyrosine derivatives **18a** and **18b**, **20a** and **20b**, **80a** and **80b**, and **81a** and **81b**, respectively (Table 3.2). For example, the nitro-substituted analogues **71a**, **71b**, **72a** and **72b** reacted approximately four times faster than the corresponding phenylalanine derivatives **18a**, **18b**, **20a** and **20b** (Table 3.2), which corresponds to a ρ value of *ca.* +0.47 (using the $\sigma_{p(NO_2)^-}$ constant of 1.27).[190] The relative reactivity of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** is to be expected, since the transition state for a reaction of this type involves transfer of halogen to the nucleophilic stannyl radical with the development of an electron rich centre at the site of halogen abstraction (Figure 2).[29,34,192] Favourable delocalisation of the developing negative charge over the electron deficient nitro-aromatic system can occur in the reactions of the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b**, and therefore radical formation proceeds more readily than in the reactions of the corresponding bromophenylalanine and bromotyrosine derivatives **18a**, **18b**, **20a**, **20b**, **80a**, **80b**, **81a** and **81b**. Consequently, the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** react faster than the bromophenylalanine and bromotyrosine derivatives **18a**, **18b**, **20a** and **20b**, and **80a**, **80b**, **81a** and **81b**.

Whether the carboxy group is protected as an ester or an amide has little effect on the relative rates of reaction of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** with triphenyltin hydride, yet in the reactions with NBS, each of the amides **19**, **78b**, and **79b** reacted approximately five times faster than the corresponding ester **17**, **78a** or **79a**. These effects are not consistent with relief of steric constraints between the phthalimido and carboxy protecting groups in the reactions of the amides **19**, **78b**, and **79b** with NBS, resulting from the greater bulk of the amido substituent relative to the ester group, as such factors would be expected to be at least as

severe in the reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b**, where the large bromine atom is transferred to the bulky triphenyltin radical. The most obvious interpretation of the results is that the amido substituent of **19**, **78b**, and **79b**, being more electron rich than the ester group of **17**, **78a** and **79a**, facilitates reaction by interacting with the electron deficient benzylic radical centre in the bromination transition state (Figure 3.1). Consistent with this proposal, the extent of anchimeric assistance displayed by amides in ionic reactions is known to be larger than that shown by esters, as discussed in the previous Chapter.

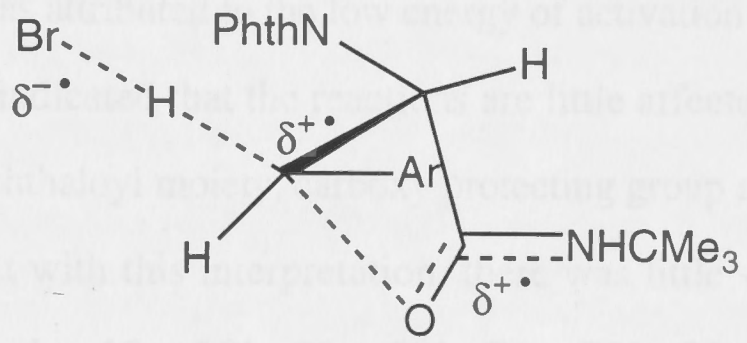


Figure 3.1. Neighbouring group participation by the amido group in the reactions with NBS to give the radicals **22**, **134b** and **135b**.

The effect of the amido group to delocalise the developing charge in the reaction transition state, as seen in the reactions of the phenylalanine derivatives **19**, **78b** and **79b** with NBS, would not be expected in the reactions of the bromides **20a**, **20b**, **72a**, **72b**, **81a** and **81b** with triphenyltin hydride, since any interaction between the carboxy group and the electron rich centre developing in the transition state would be unfavourable and would therefore be avoided (Figure 3.2).

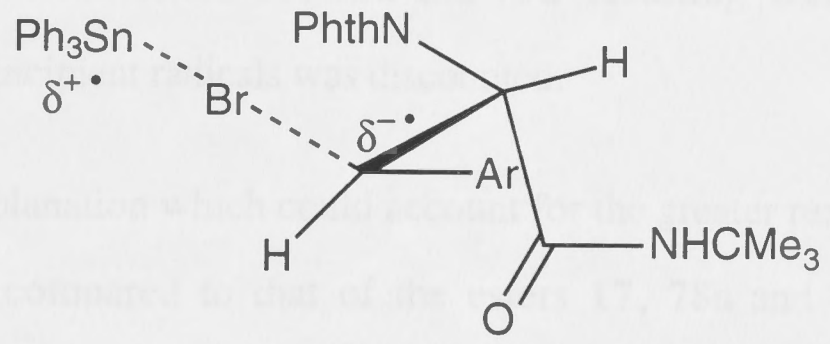


Figure 3.2. Transition state for the reactions with triphenyltin hydride to give the radicals **22**, **134b** and **135b**.

In the reactions involving NBS, the low stereoselectivity of formation of the brominated products was attributed to the low energy of activation of the halogen transfer process involved, and indicated that the reactions are little affected by steric constraints imposed by the bulky phthaloyl moiety, carboxy protecting group and aromatic side chain substituent. Consistent with this interpretation, there was little stereoselectivity in the reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** with triphenyltin hydride, which indicates these processes are also little affected by steric interactions between substituents.

Several alternative explanations which could account for the enhanced reaction rates of the amides **19**, **78b** and **79b** with NBS compared to those of the esters **17**, **78a** and **79a** (Table 3.1) were considered. While stabilisation of the developing radicals could occur through hyperconjugation with the α-carbon–carboxy carbon (C1-C2) bond, it was thought that this effect would be similar for both an ester and an amide substituent. In any case, whether the carboxy group is protected as an ester or an amide has little effect on the relative rates of reductions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** using triphenyltin hydride, reactions in which hyperconjugative stabilisation of the developing radicals could also occur. On this basis,

the explanation of the greater reactivity of the amides **19**, **78b** and **79b** with NBS compared to that of the esters **17**, **78a** and **79a** resulting from hyperconjugative stabilisation of the incipient radicals was discounted.

Another explanation which could account for the greater reactivity of the amides **19**, **78b** and **79b** compared to that of the esters **17**, **78a** and **79a** with NBS was considered which involves destabilisation of the developing partial positive charge at the benzylic position due to the inductive electron withdrawing effect of the carboxy group. Since the carboxy carbon of the ester group is more electron deficient than that of the amido substituent, it was thought that the ester moiety could destabilise the developing positive charge at the β-position in the transition state to a greater extent than the amide, thereby resulting in the greater rates of reactions of the amides **19**, **78b** and **79b** compared to those of the esters **17**, **78a** and **79a**. However, the nature of the carboxy protecting group has little effect on the rates of reactions of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** with triphenyltin hydride. In these reactions, the inductive effect of the carboxy protecting group would be to stabilise the developing negative charge at the β-carbon, which is opposite to the inductive effect expected in the reactions involving NBS, and therefore the esters **18a**, **18b**, **71a**, **71b**, **80a** and **80b** would be expected to react faster than the corresponding amides **20a**, **20b**, **72a**, **72b**, **81a** and **81b**. On this basis, the inductive effect of the carboxy group to account for the enhanced reaction rates of the amides **19**, **78b** and **79b** compared to those of the esters **17**, **78a** and **79a** with NBS was discounted.

Another rationalisation considered which might account for the greater reactivity of the amides **19**, **78b** and **79b** compared to those of the esters **17**, **78a** and **79a** in the reactions with NBS involved coordination of bromine atom to the amido substituent of the amides **19**, **78b** and **79b**, thereby aiding in the approach of the bromine atom to the reaction site and facilitating reaction (Figure 3.3). Similar three-electron-bonded species have been proposed as intermediates, for example, in the reactions of amino acids with

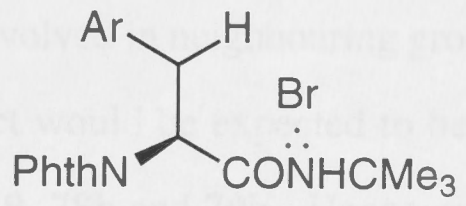


Figure 3.3. Bromine coordination to the amido substituent of the amides **19**, **78b** and **79b**.

hydroxyl radical[136] and in the radical-induced oxidation of sulfides,[137-140] and sulfide coordination of bromine atom has been demonstrated (Figure 3.4).[141]

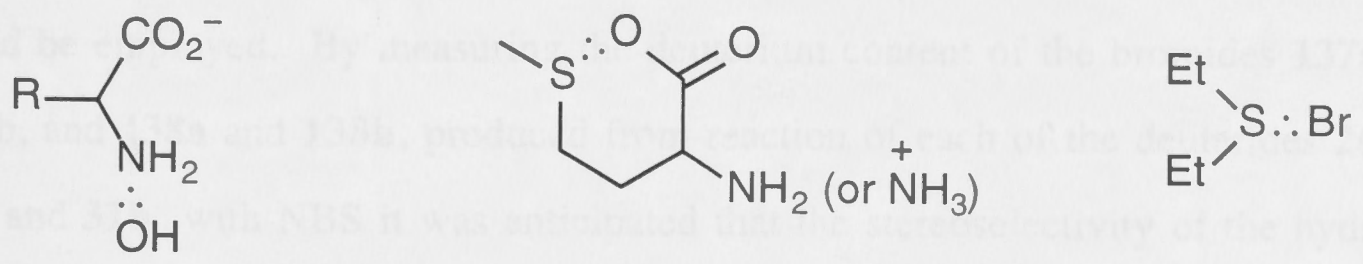
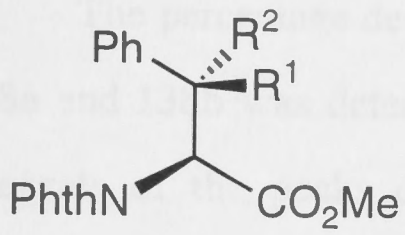


Figure 3.4. Three-electron-bonded species.

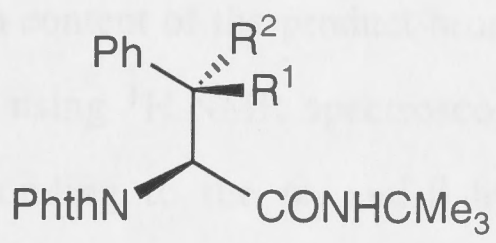
Evidence which precludes the involvement of bromine coordination to the amido substituent of the amides **19**, **78b** and **79b** in the reactions with NBS is apparent from the stereoselectivity of hydrogen abstraction in the bromination reactions, which is discussed below.

One other explanation was considered which could account for the reactivity of the phenylalanine derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** with NBS. In principal, the phthalimido group could be involved in neighbouring group participation in the reactions with NBS, although this effect would be expected to be similar for both the esters **17**, **78a** and **79a** and the amides **19**, **78b** and **79b**. Hence, participation by the phthalimido group to account for the enhanced rates of reactions of the amides **19**, **78b** and **79b** compared to those of the esters **17**, **78a** and **79a** was discounted. Further evidence precluding the involvement of the phthalimido group in the hydrogen atom transfer process is obtained from the stereoselectivity of hydrogen abstraction, which is described below.

In the bromination reactions of the phenylalanine derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b**, there was the possibility of stereoselective hydrogen abstraction. To examine this possibility, it was anticipated that the bromination reactions of the deuterated analogues **26** and **29**, and **31a** and **31b** of the phenylalanine derivatives **17** and **19** could be employed. By measuring the deuterium content of the bromides **137a** and **137b**, and **138a** and **138b**, produced from reaction of each of the deuterides **26**, **29**, **31a** and **31b** with NBS it was anticipated that the stereoselectivity of the hydrogen abstraction process could be determined. The deuterides **26**, **29**, **31a** and **31b** were already available.[58,59] Thus, the deuterides **26**, **29**, **31a** and **31b** were treated with NBS using standard bromination conditions and the percentage deuterium content determined, using ^{1}H NMR spectroscopy and mass spectrometry. In the ^{1}H NMR spectra, the deuterium content was determined from each diastereomeric bromide **137a** and **137b**, and **138a** and **138b**. In comparison, the deuterium content of the bromides **137a** and **137b**, and **138a** and **138b** was determined using mass spectrometry for the mixtures of diastereomers. The results of these experiments are shown in Table 3.4.

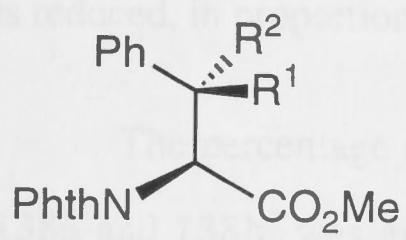


26) R^1 = D, R^2 = H
29) R^1 = H. R^2 = D



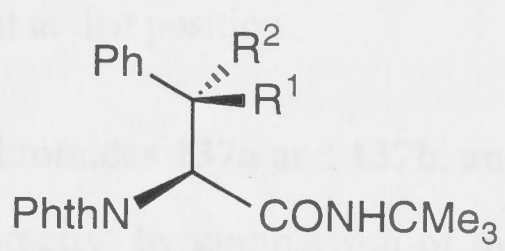
31

a) R^1 = H, R^2 = D
b) R^1 = D, R^2 = H



137

a) R^1 = D, R^2 = Br
b) R^1 = Br, R^2 = D



138

	%D			DIE			selectivity (S)		
	NMR		MS	NMR		MS	NMR		MS
comp.	**138b**	**138a**	**138a + 138b**	**138b**	**138a**	**138a + 138b**	**138b**	**138a**	**138a + 138b**
31a	82	82	77	3.26	2.97	2.61	1.40	1.53	1.28
31b	70	66	67						
31a	78	79		2.68	2.64		1.32	1.42	
31b	67	65					(pro-*R* hydrogen loss)		
	137b	**137a**	**137a + 138b**	**137b**	**137a**	**137a + 138b**	**137b**	**137a**	**137a + 138b**
26	82	83	80	5.08	5.06	4.76	1.12	1.04	1.19
29	85	84	85						
26	83	83		5.06	4.88		1.04	1.00	
29	84	83					(pro-*R* hydrogen loss)		

Table 3.4. Values of percentage deuterium content (%D), deuterium isotope effect (DIE) and selectivity (S) of hydrogen abstraction from reactions of the deuterides **26**, **29**, **31a** and **31b**.

The percentage deuterium content of the product bromides **137a** and **137b** and **138a** and **138b** was determined using ^{1}H NMR spectroscopy, from the ratio of the integrals of the peaks corresponding to the α- and β-hydrogens. The signals corresponding to the β-protons of the products are diminished relative to those of the corresponding non-deuterated analogues when those protons are replaced with deuterium and hence the integral of the β-proton signal relative to that corresponding to the α-proton is reduced, in proportion to the amount of deuterium present at that position.

The percentage deuterium content of the product bromides **137a** and **137b**, and **138a** and **138b**, was also calculated using mass spectrometry, by comparison of the mass spectra of the product mixtures with those of authentic samples of the corresponding non-deuterated analogues **18a** and **18b**, and **20a** and **20b**. In the mass spectra of the non-deuterated bromides **18a** and **18b**, and **20a** and **20b**, peaks corresponding to both the molecular ion (M_H) and the protonated molecular ion (M_H+H) are present for both the ^{79}Br and ^{81}Br isotopes. Only the peaks corresponding to ions containing the ^{79}Br isotope were used in these calculations. The mass spectra of the deuterated bromides **137a** and **137b**, and **138a** and **138b** contain peaks corresponding to the non-deuterated molecular ion (M_H), the molecular ion plus hydrogen (M_H+H) and the deuterated molecular ion (M_D), among others. The peak corresponding to the deuterated molecular ion (M_D) is coincident with the peak corresponding to the non-deuterated molecular ion plus hydrogen (M_H+H). Therefore, in order to determine the deuterium content of the products a correction for the M_H+H contribution of the peak corresponding to the deuterated ion (M_D) must be made.

The intensities of the M_H peaks relative to those of the protonated molecular ions (M_H+H) of the non-deuterated materials **18a** and **18b**, and **20a** and **20b** were measured, and using these values the corrected deuterated ion (M_D) intensity can be

calculated. From the ratio of the intensities of the peaks corresponding to the M_D and M_H ions the deuterium content of the product bromides **137a** and **137b**, and **138a** and **138b** is calculated.

Using the values of the percentage deuterium content determined from the ^{1}H NMR and mass spectra, the deuterium isotope effects and the stereoselectivity of hydrogen abstraction for reaction of the deuterides **26**, **29**, **31a** and **31b** were calculated (Table 3.4). In order to calculate the stereoselectivity of hydrogen abstraction from the data obtained in these reactions a necessary assumption is made that the deuterium isotope effects for abstraction of the pro-*R* and pro-*S* deuteriums from the deuterides **25** and **26**, and **31a** and **31b** are identical, which in the absence of neighbouring group effects, is a reasonable assumption.

The percentage deuterium content of the bromophenylalanine derivatives **137a**, **137b**, **138a** and **138b** measured from the ^{1}H NMR and mass spectra (Table 3.4) varies by less than 5% in each case. This variation can be attributed to several factors. Using ^{1}H NMR spectroscopy, errors can arise from the measurement of the integrals from which the deuterium content is determined. Errors associated with these values using this method of determination could occur from incomplete relaxation of the α- and β-protons whilst acquiring the spectral data, from measurement of the integrals of those peaks from the spectra and also from uncertainties due to baseline noise. The measurement of the integrals from the spectra is likely to be the major source of error in this case.

Uncertainties also occur in the measurement of deuterium content using mass spectroscopy. In this case, values for the deuterium content are determined from comparison of the mass spectrum of the reaction mixture with that of a non-deuterated sample. These calculations are made based on the assumption that the intensity of the molecular ion is not affected by replacing hydrogen for a deuterium. In addition, errors arise due to baseline noise, isotope peaks and in the corrections which need to be made for protonated molecular ion peaks (M+H). Furthermore, uncertainty arises as a result of

the measurement of the peak intensities from the spectra and due to variation in the operating conditions of the mass spectrometer between analysis of each sample. Therefore, given the possible sources of error in the measurement of deuterium content using these methods, the difference of less than 5% are of little significance.

The observed selectivity (S_{obs}) of the reactions of the deuterides **26**, **29**, **31a** and **31b** is dependent on the actual selectivity (S) of the hydrogen abstraction process (for reaction of non-deuterated analogues) and the deuterium isotope effect associated with cleavage of the carbon–deuterium bond. The deuterium isotope effect and actual selectivity of the hydrogen abstraction process were calculated using Equation 3.1. An example of these calculations is shown below for the reactions of the deuterides **31a** and **31b**.

Using the value of deuterium content of the bromide **138a** of 65% from reaction of the deuteride **31b** (where H_R = D), the observed selectivity ($S_{obs}(H_R/H_S)$) of hydrogen abstraction is 0.5385, whereas the value of 79% deuterium content for the bromide **138a** from reaction of the deuteride **31a** (where H_S = D) corresponds to an observed selectivity of 3.7619.

Equation 3.1 $S = S_{obs}$ (**138a** from **31b**) x DIE = S_{obs} (**138a** from **31a**) ÷ DIE

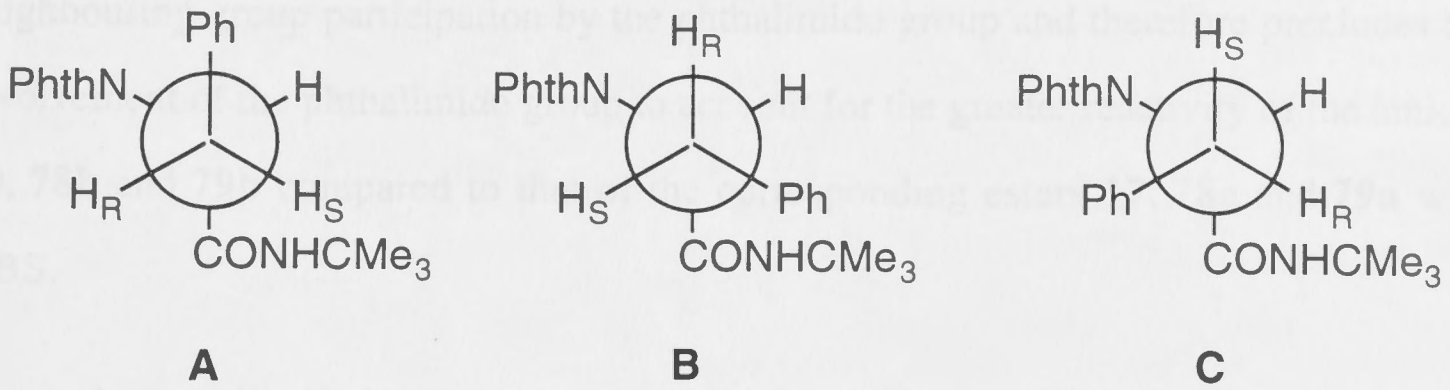
$\therefore$ $DIE^2 = (S_{obs}$ (**138a** from **31a**)) / (S_{obs} (**138a** from **31b**))

DIE^2 = 6.986, therefore DIE = *ca.* 2.64

Substituting DIE into Equation 3.1, the actual selectivity (S) = 1.42 for abstraction of the pro-*R* hydrogen.

The deuterium isotope effect of approximately 3 for the reactions of the deuterides **31a** and **31b** is much less than the isotope effect of approximately 5 for the reactions of the esters **26** and **29** and is consistent with the proposed mechanism involving interaction of the amido substituent with the radical centre in the reaction transition state. Stabilisation of the transition state by the amido group in the reactions of the amides **31a** and **31b** and hence lowering of the energy of the transition state species relative to that in the reaction of the esters **26** and **29** results in a decrease in the difference between the zero point energies of the carbon-hydrogen and carbon-deuterium bonds and a diminished deuterium isotope effect for reaction of the amides **31a** and **31b**. Since radical hydrogen abstraction processes occur with relatively little bond cleavage in the transition state, the difference in the deuterium isotope effects for the reactions of the esters **26** and **29** and the amides **31a** and **31b** can be rationalised in terms of the relative extent of bond cleavage in the reaction transition states for each of the processes. The reactions of the amides **31a** and **31b** involve a lower isotope effect than those of the esters **26** and **29**, which indicates that the former reactions occur with less bond cleavage at the transition state,[24] consistent with neighbouring group participation by the amido substituent.

The experiments described above involving the deuterides **26**, **29**, **31a** and **31b** indicate that the stereoselectivity of hydrogen abstraction in the reaction of the amide **19** is greater than that in the reaction of the ester **17**, which is consistent with neighbouring group participation by the amido substituent in the reaction of the amide **19** to facilitate hydrogen abstraction and radical formation, as shown in Figure 3.1. Considering the conformations **B** and **C** of **19** which have the correct orientation to undergo hydrogen atom transfer with direct interaction between the amide group and the developing electron deficient centre, unfavourable steric interactions between the bulky phenyl and phthaloyl substituents are present in the conformation **C**. Consequently, the conformer **B** is likely to be preferred on steric grounds, and in this orientation stereoselective loss of the pro-*R* hydrogen would be expected.



(relative stereochemistry shown only)

Figure 3.5. Staggered conformations of the amide **19**.

The pro-*R* selectivity of hydrogen abstraction in the reaction of the phenylalaninamide **19** is not simply a result of steric effects. The ^{1}H n.m.r. spectra of the amides **31a** and **31b**, and the respective coupling constants, $J_{\alpha,\beta}$, of 9.8 and 5.8 Hz, indicate that the preferred conformation of the (*S*)-enantiomer of **19** is **A**. This is the only staggered conformation which will give rise to the large coupling constant between the α-proton and the pro-*R* β-hydrogen. In this conformation, any steric interactions affecting the hydrogen atom transfer would be expected to result in stereoselective loss of the pro-*S* hydrogen, as this site is the least hindered to approach of bromine atom and loss of this hydrogen would relieve steric interactions between the phenyl and phthalimido groups.

Participation by the phthaloyl group in the hydrogen atom transfer process would be expected to result in stereoselective loss of the pro-*S* hydrogen. This would occur from the conformer **A**, whereas loss of the pro-*R* hydrogen would involve the conformer **C**. Not only is the conformer **C** of much higher ground state energy, but reaction *via* that conformer would also involve the development of additional steric interactions between

the phenyl and phthaloyl substituents in the transition state. Hence, the selectivity for abstraction of the pro-*R* hydrogen in the reaction of the amide **19** is inconsistent with neighbouring group participation by the phthalimido group and therefore precludes the involvement of the phthalimido group to account for the greater reactivity of the amides **19**, **78b** and **79b** compared to that of the corresponding esters **17**, **78a** and **79a** with NBS.

As mentioned above, one explanation that was considered which could account for the greater reactivity of the amides **19**, **78b** and **79b** compared to that of the corresponding esters **17**, **78a** and **79a** with NBS involved coordination of bromine atom to the amido substituent of the amides **19**, **78b** and **79b**. Coordination of bromine atom and subsequent reaction with the amide **19** in the conformation **C** (Figure 3.5) is unlikely due to unfavourable steric crowding between the phenyl and phthaloyl substituents. Hence, reaction of coordinated bromine is most likely to occur in the conformers **A** and **B**. In the conformer **A**, abstraction of either the pro-*R* or pro-*S* hydrogen by coordinated bromine appears equally likely, whilst abstraction of only the pro-*S* hydrogen could occur in the conformation **B**. Therefore, coordination of bromine atom to the amido group would be expected to result in preferential abstraction of the pro-*S* hydrogen. However, preferential removal of the pro-*S* hydrogen is opposite to the stereoselectivity of hydrogen abstraction in the reaction of the amide **19**, determined from the reactions of the deuterides **31a** and **31b** with NBS, and suggests that the reactions involving NBS do not occur with coordination of bromine to the amido group.

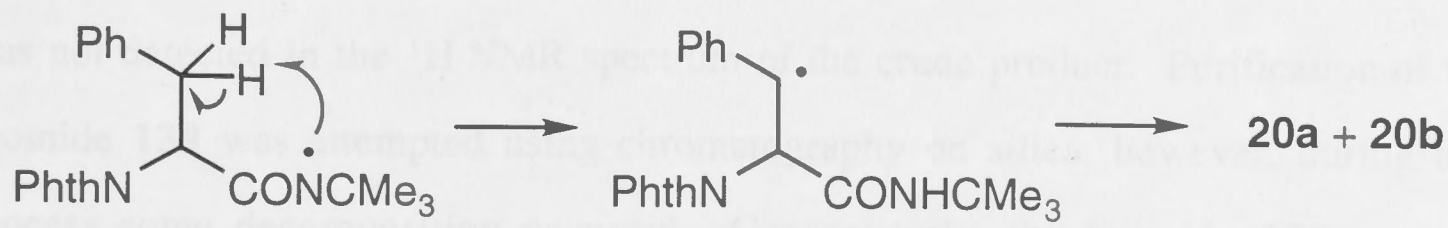
In conclusion, all of the above evidence indicates that the reactions of the phenylalanine derivatives **19**, **78b** and **79b** with NBS involve anchimeric assistance in hydrogen atom abstraction by bromine atom, through neighbouring group participation by the adjacent protected carboxy group. It appears that this may be a more specific phenomenon than the examples of 1,3-participation in atom transfer reactions reported previously.[61,144-148] While 1,3-participation occurs in reactions involving either

hydrogen or halogen atom abstraction, with correspondingly electron rich or deficient transition states, neighbouring group effects observed in the present work are apparently limited to hydrogen transfer reactions and the stabilisation of electron deficient reaction transition states.

RESULTS AND DISCUSSION: CHAPTER 4

1,4-Hydrogen Transfer Reaction of an *N*-Bromophenylalaninamide Derivative

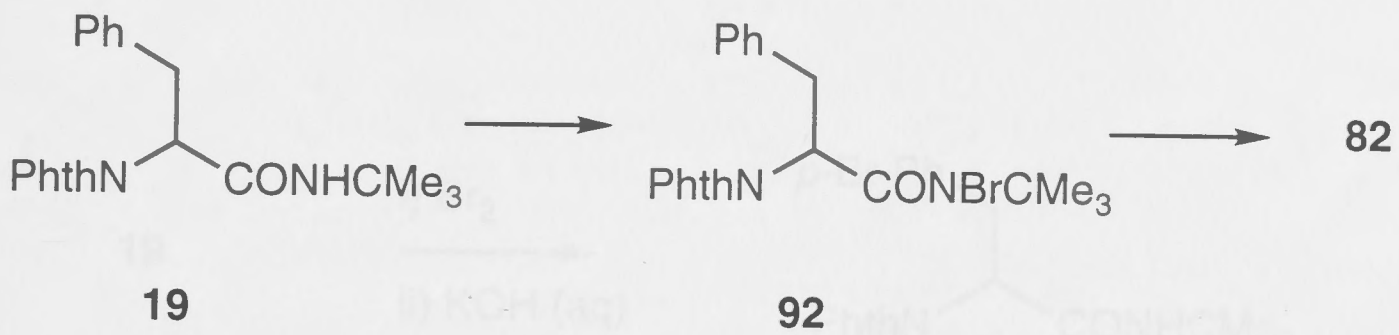
In the previous Chapter, side chain bromination reactions of the amino acid derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** were investigated. In these reactions, the rate of hydrogen atom transfer was enhanced when the carboxy group was protected as an amide, rather than an ester, which was attributed to neighbouring group participation by the amido substituent, through direct interaction with the radical centre. As part of that investigation, the remote possibility of reaction *via* an amidyl radical was considered, which had to be checked. For example, in the reaction of the phenylalanine derivative **19**, it was thought that the amidyl radical species **82** could undergo an intramolecular 1,4-hydrogen transfer from the benzylic position to give the benzylic radical **22**, which could then abstract bromine to afford the bromides **20a** and **20b** (Scheme 4.1). In this manner it was thought that the reactions of the amides **19**, **78b** and **79b** could be accelerated relative to those of the corresponding esters **17**, **78a** and **79a**, thereby accounting for the observed kinetic effects. The amidyl radical **82** of the phenylalanine derivative **19** was chosen as the substrate to investigate this possibility. Therefore, an aim of the work described in this Chapter was to investigate the possible involvement of amidyl radicals as intermediates in the reactions of the phenylalanine derived amides **19**, **78b** and **79b** with NBS.



82 **22**

Scheme 4.1

It was envisaged that the amidyl radical **82** chosen for study could be obtained from photolysis of the *N*-bromoamide **92**, which in turn could be prepared from the amide **19** (Scheme 4.2). Hence, synthesis of the *N*-bromoamide **92** was required.

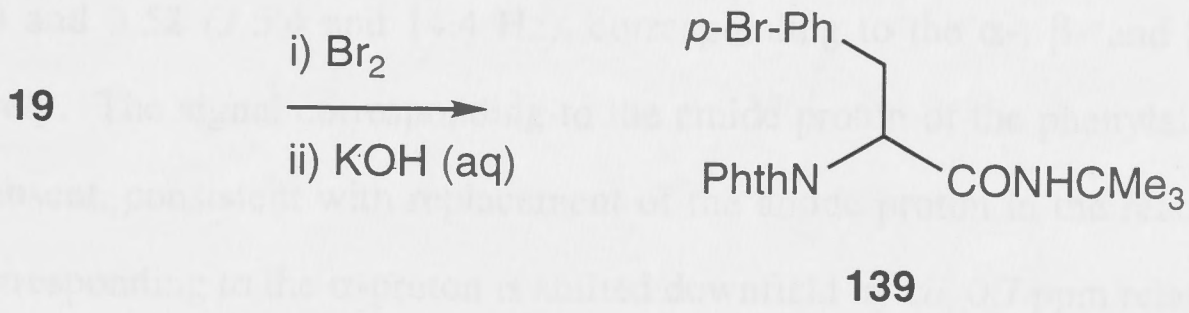


Scheme 4.2

Few methods for the synthesis of *N*-bromoamides from the corresponding amide precursors have been reported.[193-195] One procedure involves treating a solution of an amide in acetic acid with aqueous sodium bromite,[194] while other methods involve treatment of an amide with *tert*-butyl hypobromite[193,196] or molecular bromine and aqueous potassium hydroxide.[195]

Initially, preparation of the *N*-bromoamide **92** was attempted using the procedure involving bromine.[195] Accordingly, the amide **19** was dissolved in neat bromine and the solution was cooled to 0 °C, then aqueous potassium hydroxide was added. Following workup of the reaction mixture, analysis of the crude product using ^{1}H NMR spectroscopy showed that the phenylalaninamide **19** had reacted to give mainly the *p*-bromophenylalanine derivative **139** (Scheme 4.3). The *N*-bromoamide **92** was not detected in the ^{1}H NMR spectrum of the crude product. Purification of the bromide **139** was attempted using chromatography on silica, however, during this process some decomposition occurred. Consequently, the bromide **139** was not purified or characterised further. The regioselectivity of reaction was determined from the ^{1}H NMR spectrum of the crude material, which contained doublet resonances at

δ 7.31 (*J* 8.4 Hz), 7.05 (*J* 8.4 Hz) and 3.49 (*J* 8.5 Hz), and a triplet at δ 4.96 (*J* 8.5 Hz) corresponding to the two pairs of aromatic hydrogens of the substituted phenyl substituent and the β- and α-hydrogens, respectively, consistent with aromatic substitution at the *para*-position.



139

Scheme 4.3

Presumably, the bromide **139** is produced in the reaction by electrophilic aromatic substitution of the amide **19**. In general, the use of elevated temperature, strongly acidic conditions or a Lewis acid catalyst is required to achieve electrophilic aromatic substitution in non-activated aromatic systems.[197] In this case, however, the reaction was carried out in the absence of a Lewis acid catalyst, at 0 °C and in a basic medium, conditions in which electrophilic aromatic substitution of a non-activated substrate would not be expected to occur. One possible mechanism which could account for the ease of substitution involves neighbouring group participation by the amido group, through stabilisation of the arenium ion intermediate. While not pursued in the current work, it was anticipated that further investigation into this system would explain the ease of aromatic substitution.

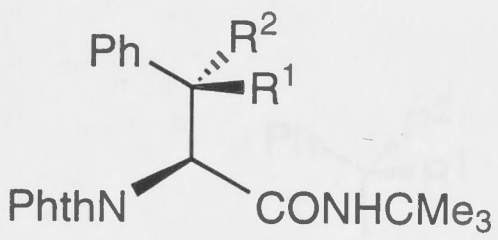
Given that preparation of the *N*-bromoamide **92** using molecular bromine was unsuccessful, an alternative procedure involving *tert*-butyl hypobromite was investigated. Accordingly, the phenylalaninamide **19** was treated with a solution of *tert*-butyl hypobromite, which was prepared using literature procedures,[193,196] at room

temperature for 16 h in the dark. Analysis of the crude product using ^{1}H NMR spectroscopy showed that the *N*-bromoamide **92** was present in high yield. Formation of the *N*-bromoamide **92** in the reaction was established from the infrared spectrum of the crude product, in which the absorbance due to the NH stretching frequency of the amide **19** was absent, and from the ^{1}H NMR spectrum. In the ^{1}H NMR spectrum, doublet of doublet resonances occurred at δ 5.69 (*J* 5.4 and 10.5 Hz), 3.59 (*J* 10.5 and 14.4 Hz) and 3.52 (*J* 5.4 and 14.4 Hz), corresponding to the α-, β- and β'-protons, respectively. The signal corresponding to the amide proton of the phenylalaninamide **19** was absent, consistent with replacement of the amide proton in the reaction. The signal corresponding to the α-proton is shifted downfield by *ca.* 0.7 ppm relative to that of the corresponding amide **19**, presumably due to the inductive electron withdrawing effect of the bromine attached to the amide nitrogen. This material was used in the subsequent photolysis reactions without purification or further characterisation.

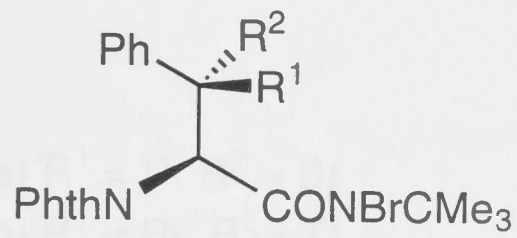
With the *N*-bromoamide **92** in hand, its photolysis reaction was investigated. Accordingly, a solution of the *N*-bromophenylalaninamide **92** in carbon tetrachloride was heated at reflux under nitrogen for 5 mins whilst being irradiated with a 300 W sunlamp. Analysis of the crude product using ^{1}H NMR spectroscopy showed that the *N*-bromoamide **92** had reacted to give mainly a 1:1 mixture of the β-bromophenylalanine derivatives **20a** and **20b**. The phenylalanine derivative **19** comprised the remainder of the material present. Thus, since photolysis of the *N*-bromoamide **92** results in formation of the bromide diastereomers **20a** and **20b**, the mechanism of reaction of the *N*-bromoamide **92**, and hence the amidyl radical **82**, could be investigated.

As described previously, an aim of the work in this Chapter was to investigate the possibility of involvement of amidyl radicals in the bromination reactions using NBS, which are described in the previous Chapter. In that work, the stereoselectivity of hydrogen abstraction from the phenylalanine derivative **19** was determined, through

investigation of the reactions of the deuterides **31a** and **31b** with NBS. In a similar manner it was anticipated that the stereoselectivity of hydrogen abstraction in the reaction of the *N*-bromoamide **92** could be determined, by investigation of the photolysis reactions of the deuterides **140a** and **140b**. If the reactions of the deuterides **31a** and **31b** with NBS proceed *via* amidyl radicals, then the stereoselectivity of hydrogen abstraction from reaction of the *N*-bromoamide derivatives **140a** and **140b** and of the deuterides **31a** and **31b** with NBS is likely to be the same. On the other hand, if the reactions of the deuterides **31a** and **31b** do not involve amidyl radical intermediates, then the stereoselectivity would be expected to be different. In order to investigate this hypothesis, preparation of the *N*-bromoamides **140a** and **140b** was required.



31



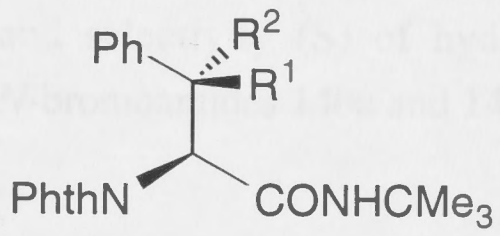
140

a) $R^1 = H$, $R^2 = D$
b) $R^1 = D$, $R^2 = H$

The deuterides **140a** and **140b** were prepared using an identical procedure to that described above for the preparation of the *N*-bromoamide **92**, by treatment of each of the deuterides **31a** and **31b**,[58] in separate experiments, with *tert*-butyl hypobromite. From these experiments, the corresponding *N*-bromoamides **140a** and **140b** were afforded in approximately 95 and 60% yields, respectively, and each with approximately 98% deuterium content as determined through ^{1}H NMR spectroscopic analysis of the crude mixtures. In each case only a single diastereomer was detected in

the ^{1}H NMR spectrum of the crude product, which suggests that no loss of chiral integrity occurs at either the α-carbon or the benzylic position during reaction. On this basis, the deuterium content of the *N*-bromoamides **140a** and **140b** is assumed to be identical to that of the starting deuterides **31a** and **31b**.[58] The deuterides **140a** and **140b** were used in the subsequent photolyses without further purification or characterisation.

Accordingly, a dilute carbon tetrachloride solution of each of the deuterides **140a** and **140b**, at a concentration of approximately 2.3 and 1.5 mM, respectively, was heated at reflux under nitrogen for 5 mins, with irradiation using a 300 W sunlamp. Analysis of the crude reaction mixtures using ^{1}H NMR spectroscopy showed that in each case the β-bromides **138a** and **138b** were produced as a 1:1 mixture of diastereomers.



138

a) R^1 = D, R^2 = Br
b) R^1 = Br, R^2 = D

The percentage deuterium in the bromides **138a** and **138b** produced from each reaction of the deuterides **140a** and **140b** was determined in a manner identical to that described in the previous Chapter for the reactions of the deuterides **31a** and **31b** with NBS, using ^{1}H NMR spectroscopy and mass spectrometry. Using ^{1}H NMR spectroscopy, the deuterium content was determined from the ratio of the integrals of the peaks corresponding to the α- and β-protons, while comparison of the mass spectrum of the bromides **138a** and **138b** with that of an authentic sample of the non-deuterated analogues **20a** and **20b** was used to calculate the deuterium content using

mass spectrometry. From these values, the deuterium isotope effect (DIE) and the selectivity of hydrogen abstraction were calculated, as described in the previous Chapter. Again, an assumption is made that the deuterium isotope effects associated with abstraction of the pro-*R* and pro-*S* deuteriums are identical. The results of these experiments are summarised in Table 4.1.

	%D			DIE			selectivity (S)		
	NMR		MS	NMR		MS	NMR		MS
comp.	**138a**	**138b**	**138a + 138b**	**138a**	**138b**	**138a + 138b**	**138a**	**138b**	**138a + 138b**
140a	23	26	28	1.64	2.16	1.48	4.46	6.15	3.81
140b	88	93	85				(pro-*S* hydrogen loss)		

Table 4.1. Percentage of deuterium retention (%D), deuterium isotope effect (DIE) and selectivity (S) of hydrogen abstraction in the reactions of the *N*-bromoamides **140a** and **140b**.

The percentage deuterium content of the bromides **138a** and **138b** calculated using ^{1}H NMR spectroscopy and mass spectrometry differed by up to 8% for the reaction of the deuteride **140b** and 5% for the reaction of the deuteride **140a**, presumably due to errors associated with the measurement of the deuterium content from the spectra, as discussed in the previous Chapter for the reactions of the deuterides **26**, **29**, **31a** and **31b** with NBS. Although the differences in these values are large, they are of little importance since it can clearly be seen that the stereoselectivity for loss of the pro-*S* hydrogen in these reactions is opposite to that in the reactions of the deuterides **31a** and **31b**, in which stereoselective loss of the pro-*R* hydrogen occurs. Hence, these results indicate that different hydrogen abstracting species are involved in each case, and that amidyl radicals are not involved in the reaction of the amide **19** with

NBS. By inference, therefore, amidyl radicals are not involved in the reactions of the amides **78b** and **79b** with NBS.

The deuterium isotope effect of approximately 1.6 obtained in the photolysis reactions of the deuterides **140a** and **140b** is significantly less than the value of approximately 2.6 obtained from the reactions of the deuterides **31a** and **31b** with NBS. A logical interpretation of this result is that the hydrogen abstracting species involved in the reactions of the *N*-bromoamides **140a** and **140b** is more reactive than that involved in the reactions with NBS, since it implies that there is less bond breaking at the transition state in the former case. However, despite the greater reactivity of the hydrogen abstracting species in the reactions of the *N*-bromides **140a** and **140b**, hydrogen abstraction occurs with greater stereoselectivity than that in the reactions of the deuterides **31a** and **31b** with NBS.

The stereoselectivity of 3.9 for removal of the pro-*S* hydrogen in the reactions of the *N*-bromoamides **140a** and **140b** is opposite to that obtained in the reactions of the deuterides **31a** and **31b** with NBS and is consistent with an intramolecular process. For intramolecular abstraction of hydrogen by the amidyl radical to occur, an eclipsed conformation of the radical species **82** is required such that the hydrogen to be abstracted and the amidyl radical centre are in close proximity. The two possible eclipsed conformations **A** and **B** in which intramolecular hydrogen abstraction by the amidyl radical can occur are shown in Figure 4.1. The preferred orientation of the radical **82** is likely to be conformation **A**, since this conformer does not involve severe steric crowding between the bulky phenyl and phthaloyl substituents present for conformer **B**. In conformer **A**, intramolecular hydrogen abstraction by the amidyl radical would result in preferential removal of the pro-*S* hydrogen, since this hydrogen is much closer to the amidyl radical centre. Hence, the stereoselectivity of hydrogen abstraction in these reactions is consistent with reaction *via* a rare intramolecular 1,4-hydrogen atom transfer.

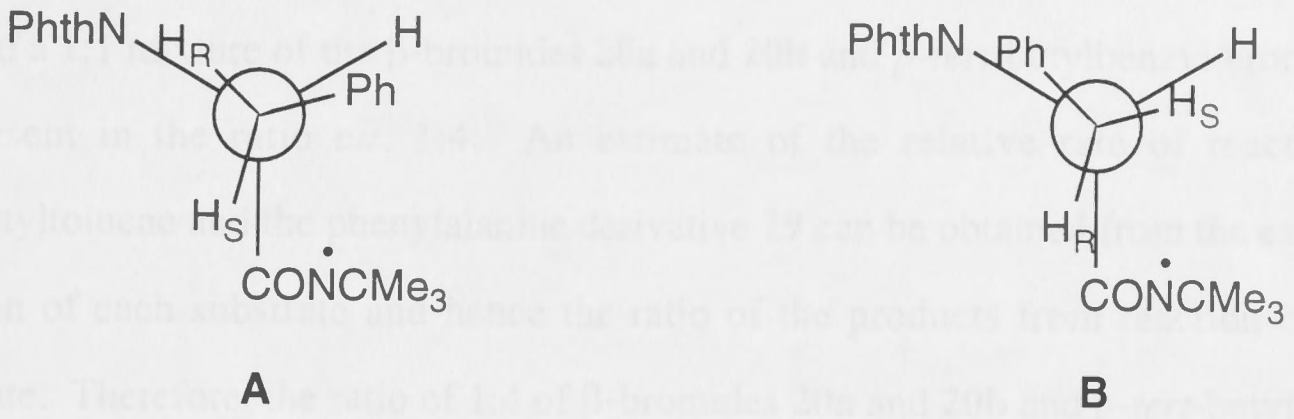


Figure 4.1. Eclipsed conformations of the radical **82** required for intramolecular hydrogen transfer.

While the stereoselectivity of hydrogen abstraction in the reactions of the deuterides **140a** and **140b** is consistent with an intramolecular reaction, it does not unambiguously establish such a process. By photolysis of mixtures of the *N*-bromoamide **92** and a competitive substrate at series of concentrations of each substrate, it was anticipated that an insight into the inter- or intramolecular mechanism of reaction of the *N*-bromoamide **92** could be gleaned, since variation in the ratio of products at different concentrations of each material will be depend upon the mechanism of reaction of the *N*-bromoamide **92**. *p-tert*-Butyltoluene was chosen as the competitive substrate in these reactions, due to the relatively low volatility and simple ^{1}H NMR spectra of that material and of the product of its bromination reaction, *p-tert*-butylbenzyl bromide.

In order to compare the reactivity of the hydrogen abstracting species involved in the reaction of the *N*-bromoamide with that in the NBS reactions, an estimate of the relative reactivity of *p-tert*-butyltoluene and the phenylalanine derivative **19** toward hydrogen abstraction by bromine atom was determined in a competitive experiment. Accordingly, an approximately equimolar amount of the phenylalanine derivative **19** and *p-tert*-butyltoluene was treated with NBS, using standard radical bromination

conditions. Analysis of the crude product of the reaction using ^{1}H NMR spectroscopy showed a 1:1 mixture of the β-bromides **20a** and **20b** and *p-tert*-butylbenzyl bromide to be present in the ratio *ca.* 1:4. An estimate of the relative rate of reaction of *tert*-butyltoluene and the phenylalanine derivative **19** can be obtained from the extent of reaction of each substrate and hence the ratio of the products from reaction of each substrate. Therefore, the ratio of 1:4 of β-bromides **20a** and **20b** and *p-tert*-butylbenzyl bromide indicates that the rate of reaction of *tert*-butyltoluene is approximately four times that of the phenylalanine derivative **19** (Table 4.2).

substrate	k_{rel} (NBS)
19	1[†]
p-MePhCMe$_3$	4

[†]Assigned as unity within column.

Table 4.2. Relative rates of reaction of the phenylalanine derivative **19** and *p-tert*-butyltoluene (*p*-MePhCMe$_3$) with NBS.

The greater reactivity of *tert*-butyltoluene toward hydrogen abstraction by bromine atom than the phenylalanine derivative **19** presumably is due to stereoelectronic effects.[24] For benzylic hydrogen abstraction, maximum radical stabilisation occurs when the carbon-hydrogen bond being cleaved is perpendicular to the aromatic ring, such that delocalisation of the developing radical with the aromatic π-system occurs. As the steric bulk of the substituents at the benzylic position increases, the perpendicular orientation of the carbon-hydrogen bond to be cleaved and the aromatic ring cannot be attained and a slower rate of radical formation results.[24] The benzylic substituent of the phenylalanine derivative **19** is much larger than the

hydrogens of *tert*-butyltoluene. Consequently, maximum delocalisation of the incipient benzylic radical onto the side chain π-system of the phenylalanine derivative **19** cannot be attained, and hence *tert*-butyltoluene reacts faster.

Having established the relative reactivity of *p-tert*-butyltoluene and the phenylalanine derivative **19** towards NBS, the photolysis reactions of the *N*-bromoamide **92** in the presence of *tert*-butyltoluene at a series of concentrations of each starting material were carried out. The sample of the *N*-bromoamide **92** used in these experiments was freshly prepared and contained approximately 20% of the amide **19**. Portions of this material were taken for use in each experiment and dissolved in solutions of *tert*-butyltoluene in carbon tetrachloride, then photolysed for 5 mins. The crude mixtures were analysed using ^{1}H NMR spectroscopy and from the ^{1}H NMR spectra the ratio of the products of reaction of each starting material was measured from the integrals of peaks characteristic of those products. The results of these experiments are shown in Table 4.3.

	[*tert*-butyltoluene]		
[**92**]	0.92 mM	1.84 mM	3.46 mM
0.65 mM	15.6 : 1	9.4 : 1	4.1 : 1
1.30 mM	24.0 : 1	13.5 : 1	9.2 : 1
2.60 mM	32.4 : 1	20.0 : 1	12.9 : 1

Table 4.3. Ratio of the bromophenylalaninamides **20a** and **20b** to *p-tert*-butylbenzyl bromide from photolysis of mixtures of the *N*-bromoamide **92** and *tert*-butyltoluene at varying concentrations.

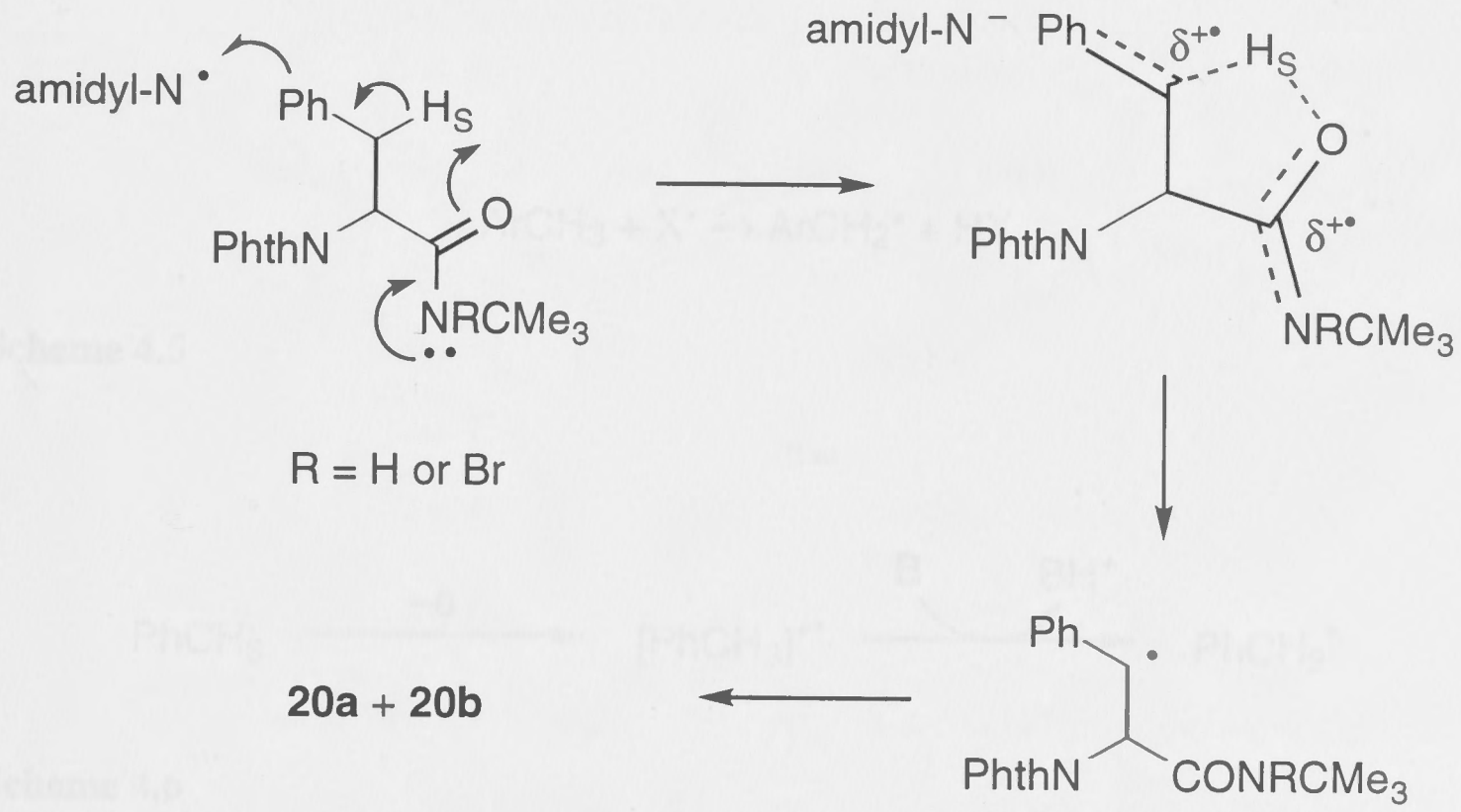
In each of these experiments, the *N*-bromoamide **92** reacted to give mainly the β-bromides **20a** and **20b**, which is in direct contrast to the reaction of the phenylalaninamide **19** and *tert*-butyltoluene with NBS, described above. In that reaction, *tert*-butylbenzyl bromide was the major product of the reaction. Hence, this result indicates that the β-position of the *N*-bromoamide **92** is much more reactive toward hydrogen abstraction than the β-position of the phenylalanine derivative **19** in the reaction with NBS, consistent with an intramolecular process. In addition, this result provides further evidence precluding the involvement of amidyl radicals in the bromination reactions using NBS.

The data shown in Table 4.3 display two general trends. Firstly, at low concentration of the *N*-bromoamide **92**, (see first row of Table 4.3) the amount of *tert*-butylbenzyl bromide produced in the reactions increases in approximate proportion to the increase in the concentration of *tert*-butyltoluene, consistent with formation of this material by an intermolecular process. A similar trend is apparent at higher concentrations of the *N*-bromoamide **92** (rows 2 and 3 of Table 4.3), although in these cases the increase in the amount of *tert*-butylbenzyl bromide produced is not in proportion to its increase in concentration. Secondly, as the concentration of the *N*-bromoamide **92** is increased (down each column), the ratio of the bromoamides **20a** and **20b** to *tert*-butylbenzyl bromide also increases. However, the increase in the amount of *tert*-butylbenzyl bromide in the mixtures is not in proportion to the increase in the *N*-bromoamide **92** concentration. Hence, this result indicates that the bromides **20a** and **20b** are formed from reaction of the *N*-bromoamide **92** *via* a mechanism involving both intermolecular and intramolecular components.

In summary, the greater reactivity of the benzylic hydrogens of the *N*-bromoamide **92** compared to those of *tert*-butyltoluene in the concentration experiments described above is consistent with an intramolecular process. In addition, the stereoselectivity of hydrogen abstraction determined from the photolysis reactions

of the deuterides **140a** and **140b** is consistent with an intramolecular reaction. However, the concentration experiments indicate that the *N*-bromoamide **92** reacts to give the bromides **20a** and **20b** *via* a mechanism which comprises both intermolecular and intramolecular components.

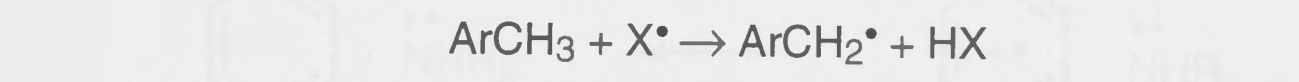
To account for these results, it is proposed that intermolecular electron transfer from the aromatic phenyl substituent to the amidyl radical (amidyl-N•) occurs with intramolecular deprotonation at the benzylic position by the basic amido group (Scheme 4.4).



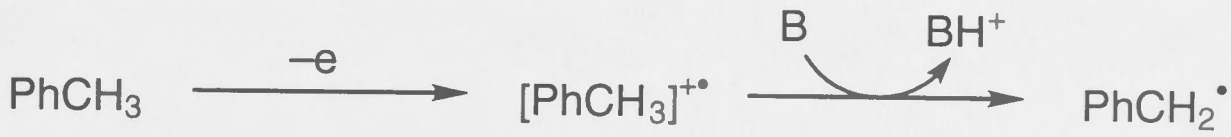
Scheme 4.4

The electron transfer component of the proposed mechanism of reaction of the *N*-bromoamide **92** (Scheme 4.4) is consistent with the mechanism of side chain oxidation of alkylbenzenes, in which electron transfer processes can play an important role.[198,199] The key step in these processes generally involves cleavage of a benzylic

carbon-hydrogen bond, with formation of a benzylic radical (Scheme 4.5) [where $X^{\bullet}$ is a generic one-electron reactant].[200] However, competition can occur between hydrogen atom transfer and a two step mechanism involving first an electron transfer resulting in the formation of a radical cation, which is then deprotonated in the second step (Scheme 4.6).[200-202] Aryl radical cations are known to be efficient sources of benzylic radicals, for example, from the photoelectron transfer reactions of phthalimides.[203,204] Hence, aryl radical cations are highly acidic species. The competition between hydrogen atom transfer (Scheme 4.4) and the process involving electron transfer (Scheme 4.5) will be determined mainly by the relative redox potential of $ArCH_3$ and $X^{\bullet}$, as well as by the strength of the HX bond and by the solvent, although the reorganisation energy associated with the electron transfer step can also play an important role.[200]



Scheme 4.5



Scheme 4.6

Electrophilic radicals may be specifically solvated by formation of complexes with electron rich solvents.[205,206] A common example of this phenomenon involves complexation of chlorine atom to benzene (Figure 4.2) or carbon disulfide. The bonding of chlorine atoms to aromatic solvents probably has the character of a charge-transfer complex,[206] with the chlorine atom acting as the acceptor and the solvent acting as a donor (Figure 4.2).

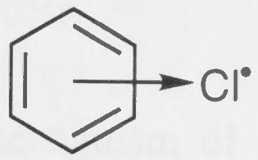


Figure 4.2. Chlorine atom complex with benzene.

Similarly, complexation of aminyl radical cations to aromatic systems has also been proposed, in the homolytic amination of aromatic substrates.[207] As with complexes formed between an aromatic solvent and chlorine atom, an intermediate in this process similar to a charge-transfer complex has been ascribed (Figure 4.3).[207]

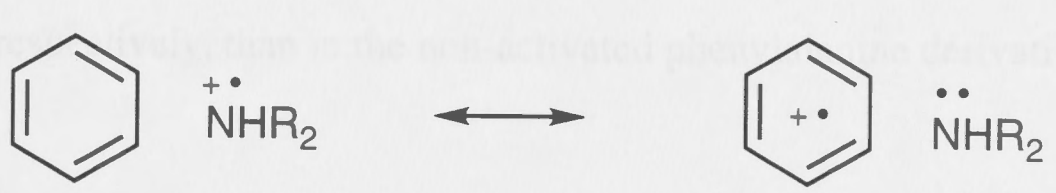
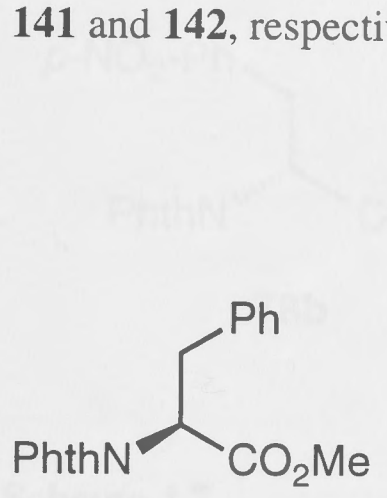


Figure 4.3. Complex formation between an aminyl radical cation and benzene.

Thus, presumably coordination of the amidyl radical **82** to the phenyl substituent in the reaction of the *N*-bromoamide **92** occurs in a similar manner to complexation of chlorine atom and aminyl radical cations with aromatic systems, with subsequent electron transfer resulting in the development of positive charge on the aromatic moiety. A consequence of this charge development in the reaction of the *N*-bromoamide **92** is that the side chain β-hydrogens become more acidic, thereby facilitating deprotonation at the benzylic position by the basic amido group (Scheme 4.4). Hence, complexation and electron transfer between the amidyl radical and the phenyl substituent of the side chain would account for the intermolecular component of

the reaction, whilst deprotonation by the basic amido group would account for the intramolecular component of the process.

Given that the proposed mechanism of reaction of the *N*-bromoamide **92** involves development of positive charge in the aromatic system, the process is likely to be disfavoured by an electron withdrawing aromatic substituent, due to the destabilising influence of that substituent on the developing charge in that system. An illustration of the dependence of similar electron transfer processes involving development of partial positive charge on the nature of the donor aromatic system was shown by Griesbeck *et al.*[172] in the photochemistry of various phthalimides. In that work, investigation of reactions of the phenylalanine, tyrosine and dihydroxyphenylalanine (DOPA) derivatives **89**, **141** and **142**, respectively, revealed that electron transfer occurred much more readily in the activated aromatic systems of the tyrosine and DOPA derivatives **141** and **142**, respectively, than in the non-activated phenylalanine derivative **89**.



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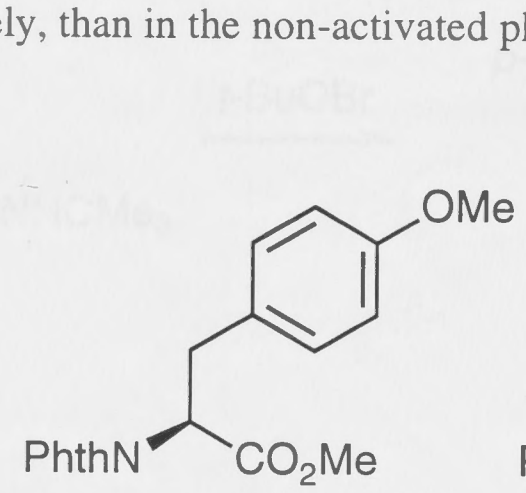

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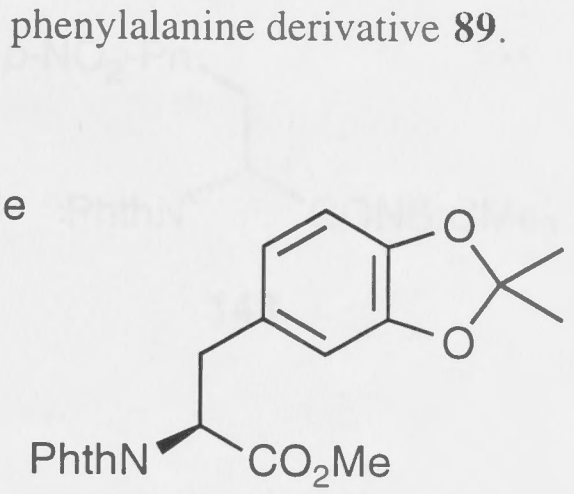
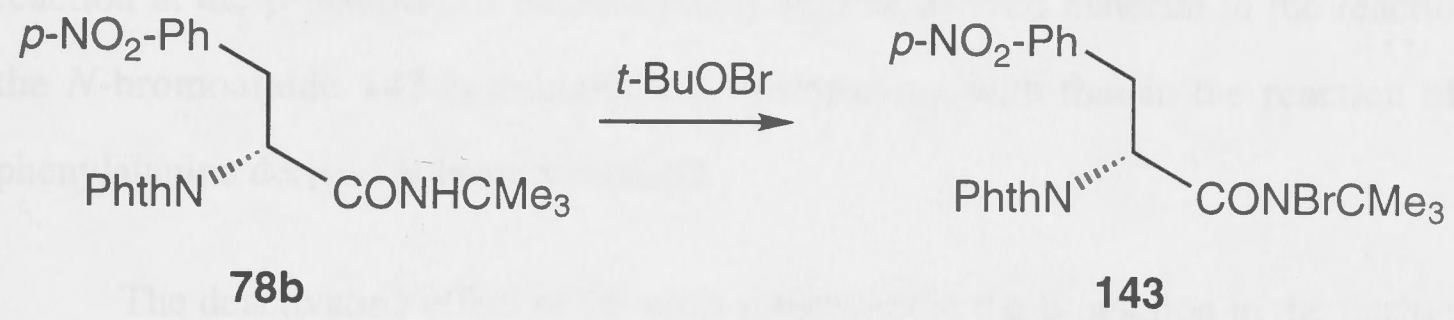


142

Given the influence of the nature of the side chain aromatic substituent on the electron transfer processes reported by Griesbeck *et al.*,[172] it was anticipated that the electron transfer process in the reaction of the *N*-bromoamide **92** could also be affected by side chain aromatic substituents. In order to investigate this possibility, the nitrophenylalanine derived *N*-bromoamide **143** was chosen for study, due to the presence of the electron withdrawing nitro substituent. Hence, the *N*-bromoamide **143**

was prepared from the nitrophenylalanine derivative **78b** (Scheme 4.7) by treatment with *tert*-butyl hypobromite, using the procedure described above, and identified from the ^{1}H NMR spectrum of the crude product of reaction. In the ^{1}H NMR spectrum, a doublet of doublet resonance occurred at δ 5.66 (*J* 6.6 and 9.3 Hz), corresponding to the α-proton, which is very similar to the chemical shifts of the signals corresponding to the α-protons of the *N*-bromoamides **92**, **140a** and **140b**, described above. Consistent with formation of the *N*-bromoamide **143**, the signal corresponding to the amide proton of the derivative **78b** was absent from the ^{1}H NMR spectrum of the crude material. This material was used in the subsequent photolysis without purification or further characterisation.



78b **143**

Scheme 4.7

A solution of the *N*-bromoamide **143**, at a concentration of approximately 1.5 mM, and *ca.* 1.3 molar equivalents of *tert*-butyltoluene, in the ratio *ca.* 1:1.3, was photolysed using the conditions described above for the reactions of the *N*-bromoamide **92**. Analysis of the crude product using ^{1}H NMR spectroscopy showed that a 1:1 mixture of the bromides **72a** and **72b** and *p-tert*-butylbenzyl bromide were present in the ratio 6.6:1. From this ratio, an estimate of the relative rate of formation of the products of the reaction of the *N*-bromoamide **143** and *tert*-butyltoluene was

determined. Hence, allowing for the excess of *tert*-butyltoluene in the initial mixture, the rate of formation of the bromides **72a** and **72b** is estimated at approximately 8.6 times that of *tert*-butylbenzyl bromide.

The nitro-substituted *N*-bromoamide **143** reacted to give the corresponding bromides **72a** and **72b** considerably less efficiently than the reaction of the *N*-bromophenylalanine derivative **92** to give the β-bromides **20a** and **20b**, presumably due to the electron withdrawing influence of the nitro-aromatic substituent. For example, whereas photolysis of the *N*-bromoamide **92** and *tert*-butyltoluene, in the ratio 1:1.4, afforded a 1:1 mixture of the bromides **20a** and **20b** and *tert*-butylbenzyl bromide in the ratio 15.6:1 (Table 4.3), the nitrophenylalanine derivative **143** reacted with 1.3 molar equivalents of *tert*-butyltoluene to give the corresponding bromides **72a** and **72b** and *tert*-butylbenzyl bromide in the ratio 6.6:1. Hence, it can clearly be seen that reaction at the β-position of the nitrophenylalanine derived material in the reaction of the *N*-bromoamide **143** is diminished in comparison with that in the reaction of the phenylalanine derived *N*-bromoamide **92**.

The deactivating effect of the nitro substituent at the β-position in the reaction of the *N*-bromoamide **143** is consistent with that seen in the bromination reactions described in the previous Chapter, in which the nitro substituted derivatives **78a** and **78b** reacted slower than the corresponding phenylalanine derivatives **17** and **19**. In addition, the deactivating influence of the nitro group is consistent with the mechanism proposed for reaction of the *N*-bromoamide **92** (Scheme 4.4) involving electron transfer to electrophilic amidyl radical with positive charge development in the aromatic side chain substituent.

In conclusion, the involvement of amidyl radicals as intermediates in the reactions of the phenylalanine derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** with NBS has been precluded, through investigation of the reactions of the *N*-bromophenylalanine derivatives **92**, **140a** and **140b**, in which the stereoselectivity of hydrogen abstraction

was opposite to that in the reactions of the phenylalanine derivatives **31a** and **31b**. The *N*-bromophenylalaninamide derivative **92** was determined to react *via* a process involving intermolecular and intramolecular components. A mechanism involving intermolecular electron transfer followed by intramolecular proton abstraction by the basic amido group was proposed to account for these results.

RESULTS AND DISCUSSION: CHAPTER 5

p-Methylphenylalanine Derivatives as Probes to Investigate Neighbouring Group Participation in Side Chain Bromination Reactions of Amino Acid Derivatives

The rates of the side chain radical bromination reactions of the phenylalanine derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** discussed in Chapter 3 of the Results and Discussion of this thesis were dramatically affected by the nature of the carboxy protecting group. The amides **19**, **78b** and **79b** reacted approximately 5 times faster than the corresponding esters **17**, **78a** and **79a**, which was attributed to direct interaction of the amido substituents with the developing benzylic radical centres in the electron deficient transition states. In the previous Chapter, the photolysis reaction of the *N*-bromoamide **92** was examined in order to check the possibility of involvement of amidyl radicals as intermediates in the bromination reactions described in Chapter 3. In that work, the *N*-bromoamide **92** was determined to react *via* a mechanism involving electron transfer on the aromatic side chain substituent, which prompted the current investigation into the possible involvement of the aromatic side chain substituent in the radical bromination reactions described in Chapter 3.

It was envisaged that the amido substituent, being approximately 10^6 times more basic than an ester, could stabilise the charge developing in the benzylic system through interaction directly with the π-system as shown in Figure 5.1. In this manner it was thought that the amido substituent could facilitate the bromination reactions. The valine derivatives **95** and **96** and the *p*-methylphenylalanine derivatives **93** and **94** were chosen as substrates to investigate this possibility.

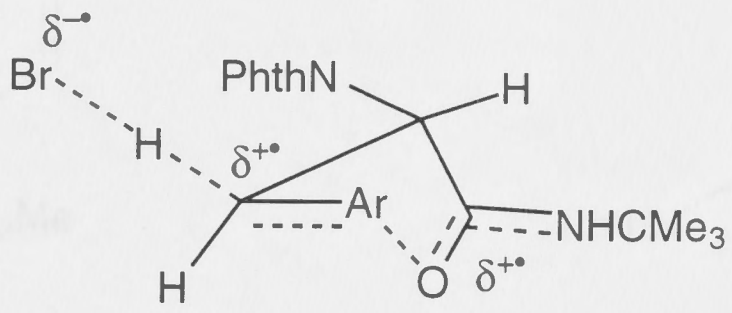
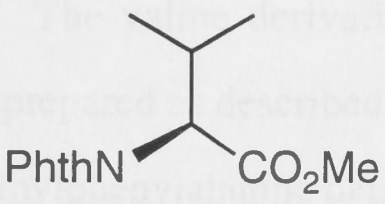


Figure 5.1. Neighbouring group participation by the amido group in the reactions to give the radicals **22**, **134b** and **135b**.

The valine derivatives **95** and **96** were chosen for study since they provide the opportunity to probe for neighbouring group participation in side chain radical bromination reactions in the absence of an aromatic side chain substituent, while the methylphenylalanine derivatives **93** and **94** were chosen since the *p*-methyl-substituent could be exploited for use as an internal standard in the reactions. For radical bromination of the *p*-methylphenylalanine derivative **94** with interaction of the amido group with the aromatic side chain, both the β-hydrogens and the *p*-methyl-hydrogens would be expected to be activated towards hydrogen atom abstraction by bromine atom relative to those of the ester **93**, and should therefore react faster. In comparison, for reaction of the amide **94** with direct interaction by the amido substituent at the benzylic position, reaction at the β-position would be expected to occur faster than that of the β-position of the ester **93**, whereas the rates of reactions at the *p*-methyl-substituents would be unaffected by the nature of the carboxy group.



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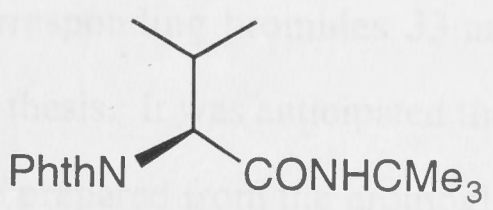

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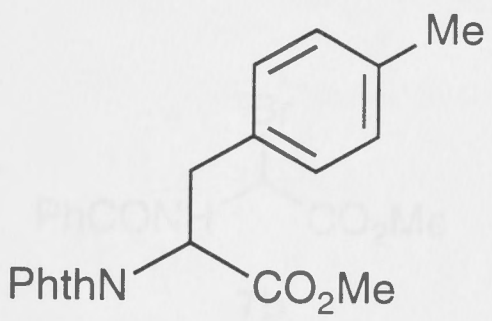

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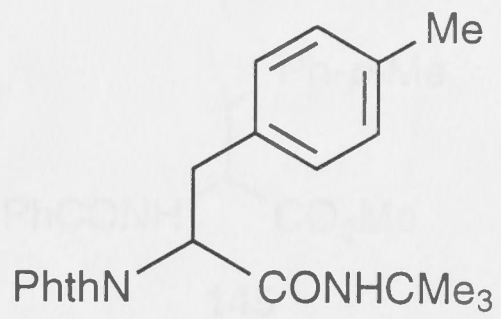
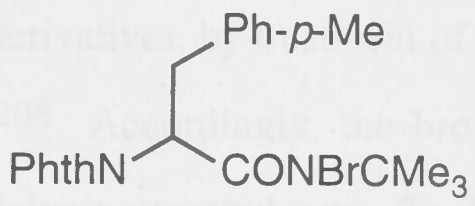


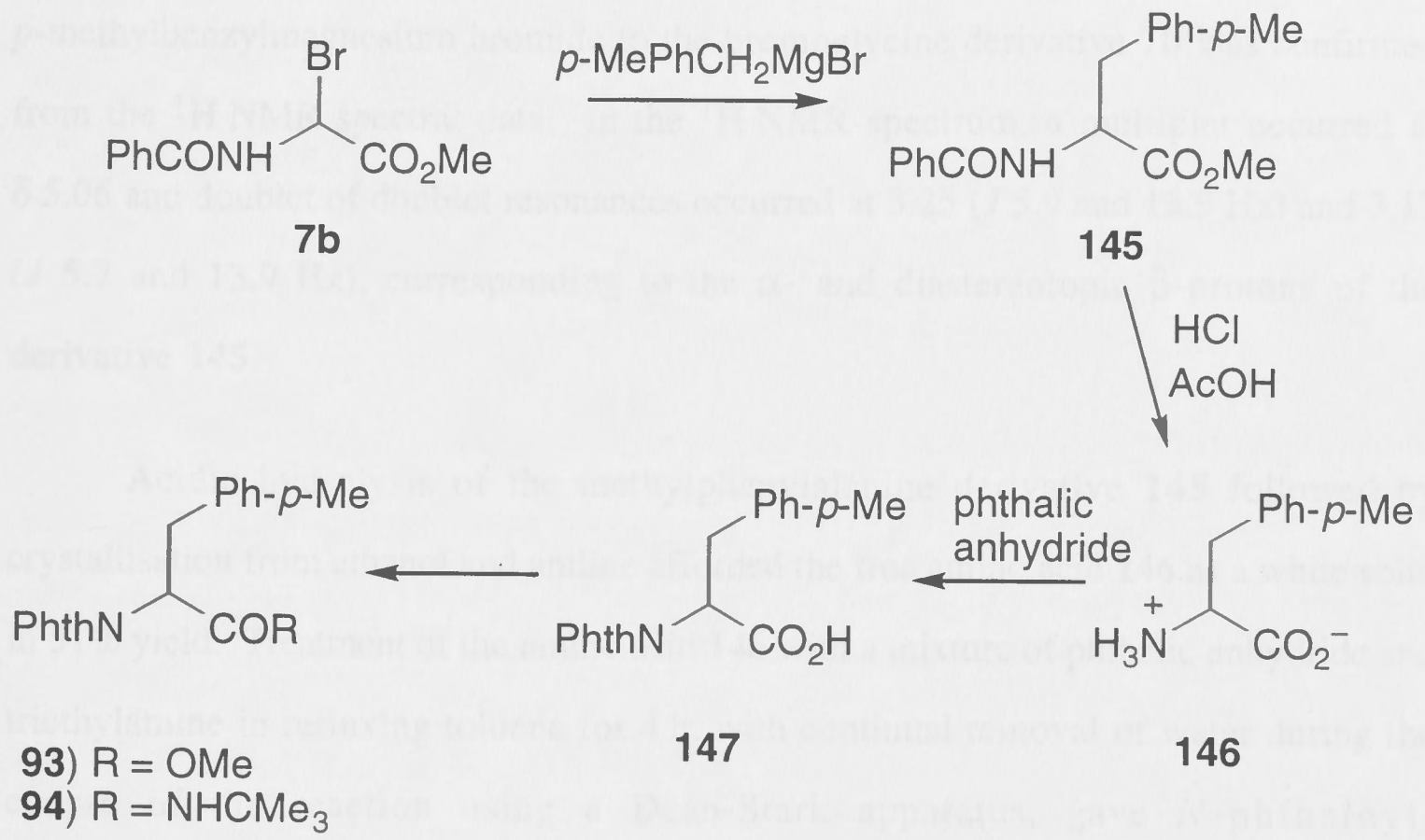
94

In addition to using the methylphenylalanine derivative **94** to investigate the bromination reactions involving NBS, it was envisaged that the amide **94** could be utilised to examine the role of the aromatic side chain substituent in the reaction of the *N*-bromoamide **92**, through reaction of the methylphenylalanine derived *N*-bromoamide **144**. In this case, the *p*-methyl substituent provides a probe to examine the reactivity of the β-hydrogens relative to that of the *p*-methyl hydrogens. In order to investigate these hypotheses, the valine derivatives **95** and **96** and the *p*-methylphenylalanine derivatives **93** and **94** were required.



144

The valine derivatives **95** and **96** and the corresponding bromides **33** and **73** were prepared as described in Chapters 1 and 2 of this thesis. It was anticipated that the *p*-methylphenylalanine derivatives **93** and **94** could be prepared from the bromoglycine derivative **7b** as shown in Scheme 5.1.



Scheme 5.1

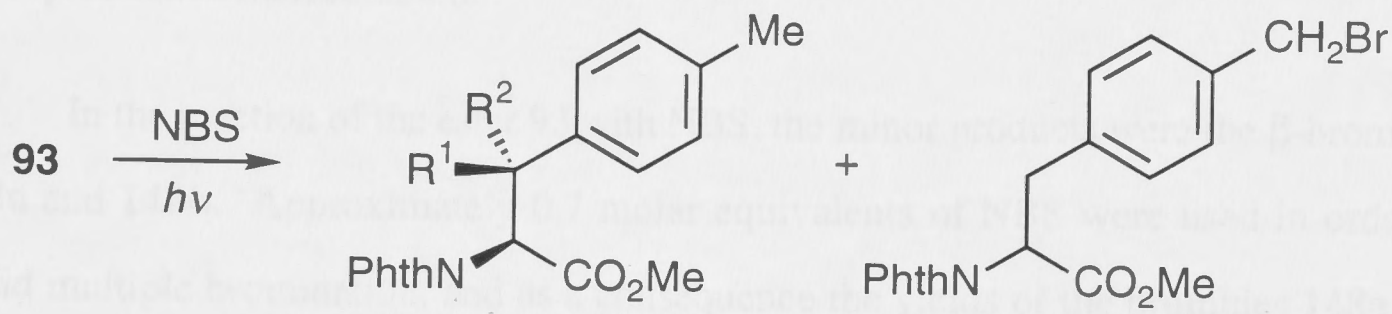
It was expected that the *N*-benzoylmethylphenylalanine derivative **145** could be prepared from the bromoglycine derivative **7b** by the addition of *p*-methylbenzylmagnesium bromide. A similar procedure has been used to prepare a variety of aliphatic and unsaturated amino acid derivatives, by treatment of bromoglycine derivatives with various Grignard reagents.[208] Accordingly, the bromoglycine derivative **7b** was synthesised from *N*-benzoylglycine methyl ester **7a**, by treatment with NBS under photolytic conditions using a standard procedure.[53] Treatment of the bromide **7b** with *p*-methylbenzylmagnesium bromide, which was prepared from two equivalents of *p*-methylbenzyl bromide and magnesium turnings, afforded the *N*-benzoyl-*p*-methylphenylalanine derivative **145** in 23% yield, after chromatography on silica. Optimisation of the yield in this reaction was not attempted, but the most likely cause of the low yield is coupling of *p*-methylbenzyl bromide with *p*-methylbenzylmagnesium bromide, since coupling of benzyl Grignard reagents with corresponding benzyl halides

is common in this type of reaction.[209] Formation of the product **145** from coupling of *p*-methylbenzylmagnesium bromide to the bromoglycine derivative **7b** was confirmed from the ^{1}H NMR spectral data. In the ^{1}H NMR spectrum, a multiplet occurred at δ 5.06 and doublet of doublet resonances occurred at 3.25 (*J* 5.9 and 13.9 Hz) and 3.17 (*J* 5.7 and 13.9 Hz), corresponding to the α- and diastereotopic β-protons of the derivative **145**.

Acidic hydrolysis of the methylphenylalanine derivative **145** followed by crystallisation from ethanol and aniline afforded the free amino acid **146** as a white solid in 51% yield. Treatment of the amino acid **146** with a mixture of phthalic anhydride and triethylamine in refluxing toluene for 4 h, with continual removal of water during the course of the reaction using a Dean-Stark apparatus, gave *N*-phthaloyl-*p*-methylphenylalanine **147** as a white solid in 97% yield. This material was identified using ^{1}H NMR spectroscopy and mass spectrometry, the latter showing a peak at *m/z* 309 corresponding to the molecular ion. In the ^{1}H NMR spectrum, peaks characteristic of a phthaloyl substituent occurred between δ 7.80-7.67, whilst a triplet occurred at δ 5.20 (*J* 8.3 Hz) and a doublet at δ 3.56 (*J* 8.3 Hz), corresponding to the α- and β-protons of the derivative **147**. From the acid **147**, the ester **93** was prepared in 88% yield by treatment with acidified methanol. The amide **94** was prepared in 97% yield by treatment of the acid **147** with thionyl chloride, and then *tert*-butylamine.

With both the ester **93** and amide **94** in hand, their reactions with NBS were investigated. Since there is a possibility of multiple bromination of either of these substrates in the reactions with NBS, less than one molar equivalent of this reagent was used. Thus, treatment of the ester **93** with NBS under standard radical bromination conditions gave a crude product containing the *p*-bromomethyl compound **149**, a 1:1 mixture of the β-bromide diastereomers **148a** and **148b** and the ester **93**. Analysis of the crude product of the reaction using ^{1}H NMR spectroscopy showed the bromide **149**, the β-bromides **148a** and **148b** and the ester **93** were present in the ratio

7.3 : 1 : 9.4. Following chromatography of the mixture on silica, the bromide **149** was isolated as a colourless oil in 30% yield.



148 **149**

a) R^1 = H, R^2 = Br
b) R^1 = Br, R^2 = H

(relative stereochemistry shown only)

Scheme 5.2

The regiochemistry of bromine incorporation in the product bromides **148a** and **148b**, and **149** was determined using ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum of the *p*-bromomethyl derivative **149**, a singlet resonance occurred at δ 4.39 corresponding to the bromomethyl moiety, while signals at δ 5.13 (dd, *J* 5.7 and 10.8 Hz) and 3.57 (m) correspond to the α- and β-protons, respectively. The peaks in the ^{1}H NMR spectrum of the ester **149** corresponding to the *p*-bromomethyl protons and the α- and β-protons were assigned by comparison with the ^{1}H NMR spectral data of the non-brominated compound **93**. The chemical shifts and splitting patterns of the signals corresponding to the α- and β-protons of the ester **149** correlate closely with those corresponding to the α- and β-protons of the starting material **93**, which is consistent with substitution at the *p*-methyl substituent. Substitution of a methyl proton with bromine is reported to cause a downfield shift of 2.2 ppm.[183] The signal corresponding to the *p*-bromomethyl group is 2.18 ppm downfield from the signal

corresponding to the *p*-methyl group of the starting amide **93**, which is in close agreement with the expected value of 2.2 ppm, and thus confirms the assignment of the peak at δ 4.39. Incorporation of a single bromine atom was apparent from the mass spectrum, which showed peaks of equal abundance at *m/z* 402 and 400, corresponding to the deprotonated molecular ion.

In the reaction of the ester **93** with NBS, the minor products were the β-bromides **148a** and **148b**. Approximately 0.7 molar equivalents of NBS were used in order to avoid multiple bromination, and as a consequence the yields of the bromides **148a** and **148b** were low. Therefore, the bromides **148a** and **148b** were not isolated, and were identified only from the ^{1}H NMR spectrum of the crude product, by comparison of the spectrum with spectral data of the corresponding bromophenylalanine derivatives **18a** and **18b**, and **25** and **28** (Table 5.1). In the ^{1}H NMR spectrum, doublets occurred at δ 5.50 (*J* 10.8 Hz) and 6.01 (*J* 10.8 Hz), which correspond to the α- and β-protons of the diastereomer **148a**. In addition, doublets occur at δ 5.59 (*J* 10.5 Hz) and 5.93 (*J* 10.5 Hz), which correspond to the α- and β-protons of the diastereomer **148b**. The ^{1}H NMR spectral data of the bromide **148a** correlate very closely with those of the bromophenylalanine derivatives **18b** and **25**, while those of the bromoester **148b** are almost identical to those of the bromides **18a** and **28**, and on this basis the bromides **148a** and **148b** were identified.

Under identical conditions to those used in the reaction of the ester **93**, the amide **94** reacted with NBS to give the β-bromide diastereomers **150a** and **150b** and the bromide **151** (Scheme 5.3). Analysis of the crude product using ^{1}H NMR spectroscopy showed the bromide **151**, a 1:1 mixture of the bromide diastereomers **150a** and **150b**, and the amide **94** in the ratio 1.4 : 1 : 4.5. Since the extent of reaction of the amide **94** was low, the yield of each of the bromides **150a**, **150b** and **151** was also low. Furthermore, the regioisomeric bromides **150a** and **150b**, and **151** were inseparable using chromatography on silica, and consequently were identified from the ^{1}H NMR

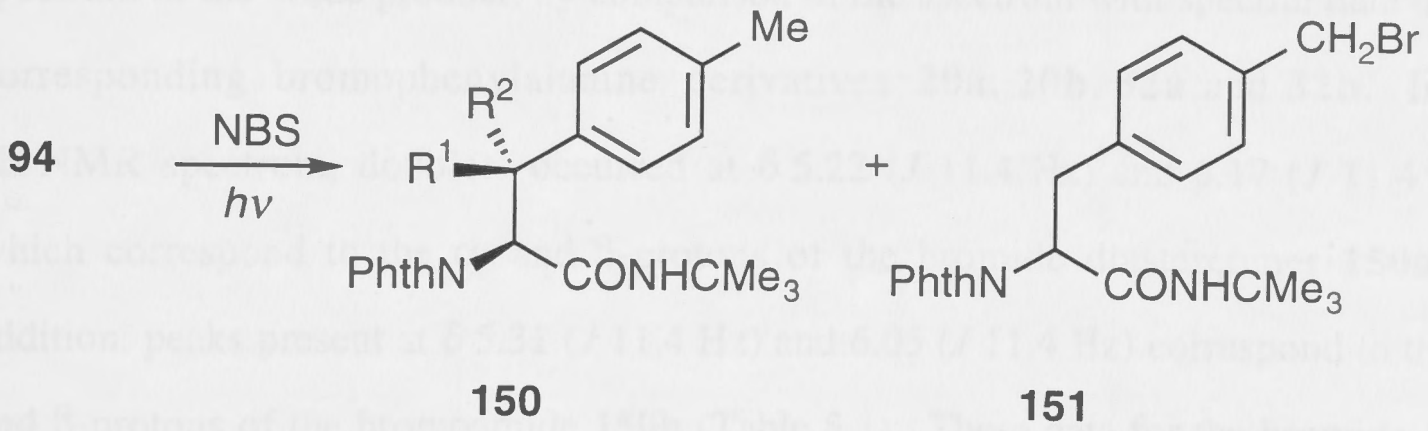
spectral data obtained from the crude reaction mixture, by comparison with the corresponding bromophenylalanine derivatives **20a**, **20b**, **32a** and **32b**, and the *p*-bromomethyl derivative **149**, as described below.

	α	β	$J_{\alpha,\beta}$	R[a]		α	β	$J_{\alpha,\beta}$	R[a]
18b	5.52	6.02	11.2	3.55	**18a**	5.59	5.91	10.5	3.82
25[b]	5.52	6.02	11.2	3.55	**28**[b]	5.59	5.91	10.5	3.82
148a	5.50	6.01	10.8	3.56	**148b**	5.59	5.93	10.5	3.81
20b	5.22	6.17	11.8	1.02	**20a**	5.32	6.05	11.4	1.40
32b[b]	5.22	6.17	11.8	1.02	**32a**[b]	5.32	6.05	11.4	1.40
150a	5.22	6.17	11.4	1.03	**150b**	5.31	6.05	11.4	1.40

[a] R values correspond to the signals of the carboxy protecting group.

[b] Data from reference 59.

Table 5.1. ^{1}H NMR spectral data of the bromophenylalanine derivatives **18a**, **18b**, **20a**, **20b**, **25**, **28**, **32a** and **32b** and the β-bromomethylphenylalanine derivatives **148a**, **148b**, **150a** and **150b**.



150 **151**

a) R^1 = H, R^2 = Br
b) R^1 = Br, R^2 = H

(relative stereochemistry shown only)

Scheme 5.3

The regiochemistry of bromine incorporation in the bromides **150a** and **150b**, and **151** is apparent from their ^{1}H NMR spectral data. A singlet resonance at δ 4.38 corresponds to the *p*-bromomethyl moiety, while doublet of doublet resonances at δ 4.96 (*J* 6.6 and 9.9 Hz), 3.57 (*J* 6.6 and 14.7 Hz) and 3.43 (*J* 9.9 and 14.7 Hz) correspond to the α-proton and each of the diastereotopic β-protons, respectively, of the bromide **151**. The assignment of the peak due to the *p*-bromomethyl group was based on comparison of the ^{1}H NMR spectral data of the starting amide **94**, in an identical manner to that described above for the ester **149**. The signal corresponding to the *p*-bromomethyl group occurs 2.15 ppm downfield from the signal corresponding to the *p*-methyl group of the amide **94**, which is in close agreement with the expected value of 2.2 ppm,[183] and thus confirms the assignment of the peak at δ 4.38. In addition, the chemical shifts and coupling constants of the signals corresponding to the α- and diastereotopic β-protons are very similar to those of the amide **94**, consistent with substitution at the *p*-methyl substituent. Hence, on these bases, the bromide **151** was identified.

In a similar manner to that described above for the β-bromides **148a** and **148b**, the β-bromide diastereomers **150a** and **150b** were identified from the ^{1}H NMR spectrum of the crude product, by comparison of the spectrum with spectral data of the corresponding bromophenylalanine derivatives **20a**, **20b**, **32a** and **32b**. In the ^{1}H NMR spectrum, doublets occurred at δ 5.22 (*J* 11.4 Hz) and 6.17 (*J* 11.4 Hz), which correspond to the α- and β-protons of the bromide diastereomer **150a**. In addition, peaks present at δ 5.31 (*J* 11.4 Hz) and 6.05 (*J* 11.4 Hz) correspond to the α- and β-protons of the bromoamide **150b** (Table 5.1). These data for the bromide **150a** correlate closely to those of the bromophenylalaninamides **20b** and **32b**, while those of the bromide **150b** are almost identical to those of the bromophenylalanine derivatives **20a** and **32a**, and on this basis the bromides **150a** and **150b** were identified.

The relative rates of reaction of the valine derivatives **95** and **96** with NBS were determined in a competitive experiment in an identical manner to that described in Chapter 3 of the Results and Discussion of this thesis for the competitive reactions of the phenylalanine analogues **17**, **19**, **78a**, **78b**, **79a** and **79b**, by treating an approximately equimolar amount of each substrate **95** and **96** and *tert*-butylbenzamide with NBS and measuring the relative rates of consumption from the mixture. The relative rates obtained from this experiment were confirmed in duplicate experiments, and varied by less than 20%. In these experiments, the valine derivatives **95** and **96** reacted at the same rate.

An indication of the reliability of the relative rates was determined by analysis of the mass balance of the reactions. In all cases the starting materials **95** and **96** and the corresponding brominated products **33** and **73** comprised greater than 85% of the material present.

An estimate of the relative rates of reaction at the β-positions and the *p*-methyl substituents of the *p*-methylphenylalanine derivatives **93** and **94** can be obtained from the ratios of products in the crude reaction mixtures. The ratio of the β-bromides **148a** and **148b** to *p*-bromomethyl derivative **149** present in the crude mixture from reaction of the ester **93** was 1 : 7.3, whereas the ratio of the β-bromides **150a** and **150b** to the *p*-bromomethyl derivative **151** from reaction of the amide **94** was 1 : 1.4. Hence, these values indicate that the hydrogens of the *p*-methyl group of the ester **93** are *ca*. 7.3 times more reactive towards hydrogen abstraction by bromine atom than those at the β-position, whereas the hydrogens of the *p*-methyl group of the amide **94** are *ca*. 1.4 times more reactive than those at the β-position. From these data, it can be seen that the β-hydrogens of the amide **94** are approximately five times more reactive than those of the ester **93** relative to the corresponding *p*-methyl substituents, consistent with the relative rates of reaction of the amides **19**, **78b** and **79b** and the esters **17**, **78a** and **79a**, discussed in Chapter 3.

Although the product ratios allow an estimate of the relative reactivity of the β- and *p*-methyl hydrogens of the ester **93** and the amide **94** to be made, a comparison of the relative reactivity of the *p*-methyl substituents of the ester **93** and the amide **94** can not be obtained from these data. In order to make this comparison, the ester **93** and the amide **94** were reacted with NBS in separate experiments in the presence of the competitive substrate *tert*-butyltoluene and the relative reaction rates were determined, as described previously. The results of a typical experiment in each case are shown in Table 5.2. In these cases, the relative rates of product formation from reactions of each substrate are shown. An indication of the reliability of the results was determined by analysis of the mass balance of the reactions. In all cases the starting materials and the brominated products comprised greater than 85% of the material present, and the extent of reaction of each substrate in these experiments was between 30-65%. By maintaining a low extent of reaction, the formation of unwanted products from multiple bromination was minimised.

substrate	k_{rel} (β-H)[b]	k_{rel} (*p*-Me)[b]	k_{rel} ($MePhCMe_3$)[b]
93	0.10	1.00	2.20[a]
94	0.55	1.02	2.20

[a] Arbitrarily assigned within table.

[b] Refers to relative rate of product formation.

Table 5.2. Relative rates of reaction of the methylphenylalanine derivatives **93** and **94** (at the β-position and the *p*-methyl substituent) and *tert*-butyltoluene with NBS.

In a duplicate experiment involving the amide **94**, the relative rates of reaction varied by less than 10% from those shown (Table 5.2). In a duplicate experiment involving the ester **93**, the relative rates of formation of the bromide **149** and *p-tert*-butylbenzyl bromide varied by less than 10%, while the rate of formation of the β-bromides **148a** and **148b** relative to that of *p-tert*-butylbenzyl bromide varied by less than a factor of two. In the latter case, the large variation in the relative rate of formation can be attributed to the small amount of the bromides **148a** and **148b** produced, such that the errors associated with measurement of the integrals of the peaks characteristic of those bromides **148a** and **148b** were large.

In the competitive reactions of the *p*-methylphenylalanine derivatives **93** and **94** and *tert*-butyltoluene with NBS, the rates of reaction at the *p*-methyl substituent of the ester **93** and the amide **94** were approximately half that of *tert*-butyltoluene. Presumably, the lower rate of reaction of the *p*-methyl substituents of the ester **93** and the amide **94** compared to that of *tert*-butyltoluene is due to hindrance of the approach of bromine atom to the *p*-methyl substituent by the bulky phthaloyl and carboxy protecting groups. In addition, the hydrogens at the β-position were less reactive than those of the corresponding *p*-methyl substituent (Table 5.2), which is consistent with deactivation due to stereoelectronic effects, as described in the previous Chapter. However, it can clearly be seen that the deactivating stereoelectronic effect at the β-position is diminished by a factor of approximately 5 in the reaction of the amide **94** relative to that in the reaction of the ester **93**, consistent with neighbouring group participation by the amido substituent to stabilise the developing positive charge in the transition state at that position.

In summary, the results obtained from the reactions of the *p*-methylphenylalanine derivative **93** and **94** indicate that the greater reactivity of the amides **19**, **78b** and **79b** compared to that of the esters **17**, **78a** and **79a**, which is described in Chapter 3, results

from neighbouring group participation by the amido substituent through direct interaction with the developing positive charge at the β-position and not through interaction with the aromatic π-system.

The valinamide **96** reacted at the same rate as the ester **95** in the competitive experiments described above, indicating that the neighbouring group effect of the amido substituent to enhance the rate of bromination on the side chains of amino acid derivatives is influenced by the nature of the side chain. The neighbouring group effect in the reactions of the phenylalanine derivatives **19**, **78b** and **79b** occurs through stabilisation of the developing charge in the transition state by the amido substituent. Reactions involving benzylic hydrogen abstraction by a halogen atom such as bromine are affected by the polar nature of the processes, of which many examples have been described.[25] In these processes, the reactions occur with the development of partial positive charge at the benzylic position, which is delocalised onto the aromatic system. By comparison, bromination reactions of aliphatic substrates are influenced by polar effects to a much lesser extent than benzylic bromination reactions, such that radical stability is the dominant factor in determining the regioselectivity of the process, as seen in the relative selectivity of gas phase bromination of butane and methyl pentanoate, shown below (Table 5.3).[25,210,211] In the reaction of methyl pentanoate, bromination at C1, adjacent to the inductively electron withdrawing, resonance stabilising methoxycarbonyl substituent, occurs to a greater extent than in the reaction of butane, indicating that the stability of the product radical is the predominant factor affecting the bromination.

In contrast to the bromination of aliphatic substrates, in which radical stability is the dominant factor affecting the reactions, polar effects control benzylic bromination. For example, although the same substituents are adjacent to the reaction centre as in the reactions of butane and methyl pentanoate, the reaction of toluene with NBS occurs

	Relative selectivities			
X	X–CH_2—CH_2—CH_2—CH_3			
H—	1.0	82	82	1.0†
CH_3OCO—	41	35	71	1.0†

† C-4 assigned as unity for each compound.

Table 5.3. Relative selectivities of gas phase bromination of butane and methyl pentanoate.

approximately four times faster than that of methyl phenylacetate (Table 5.4).[28] That is, the benzylic position is deactivated towards hydrogen abstraction by bromine atom indicating that polar effects influence the hydrogen abstraction process to a greater extent than does radical stability.

substrate	k_{rel} (NBS)†
H–CH_2Ph	1.0
CH_3OCO–CH_2Ph	0.27

† Relative reactivity per hydrogen.

Table 5.4. Relative rate of reaction of toluene and methyl phenylacetate with NBS.

Hence, and by analogy with the reactions of butane and methyl pentanoate, the reactions of the valine derivatives **95** and **96** with NBS occur with very little charge development at the β-position in the reaction transition state. Since the effect of the neighbouring amido substituent in the reactions of the phenylalanine derivatives **19**, **78b**

and **79b** is to stabilise the developing partial positive charge in the transition state, the analogous effect would not be expected in the reactions of the valine derivatives **95** and **96**. Thus, this result is consistent with the neighbouring group effect of the amido substituent to stabilise the charge developing in the transition state in the reactions of the amides **19**, **78b** and **79b** through direct interaction with the radical centre.

In Chapter 3 of the Results and Discussion of this thesis, several alternative explanations were considered which could account for the greater reactivity of the amides **19**, **78b** and **79b** compared to that of the esters **17**, **78a** and **79a**, including hyperconjugative stabilisation of the developing radical by the C1-C2 bond and coordination of bromine atom to the amido group of the amides **19**, **78b** and **79b**. The valine derivatives **95** and **96** react with NBS at the same rate, which provides further evidence to preclude the involvement of hyperconjugation and bromine coordination to the amido moiety to account for the kinetic effects, since these effects would be expected to result in a greater reactivity of the amide **96** compared to that of the ester **95**.

As mentioned above, another aim of the work described in this Chapter was to utilise the *N*-bromo-*p*-methylphenylalaninamide **144** to investigate the mechanism of reaction of the *N*-bromophenylalaninamide **92**, which reacts *via* electron transfer to the amidyl radical and intramolecular deprotonation at the benzylic position by the amido group (Scheme 4.4). Given the structural limitations of the molecule (Figure 5.2), it was anticipated that β-bromination should predominate over *p*-methyl bromination in the reaction of the *N*-bromoamide **144**, since intramolecular deprotonation by the amido group can only occur at the β-position.

In order to test this hypothesis the *N*-bromoamide **144** was required, which was synthesised from the amide **94** using the procedure described in the previous Chapter for the preparation of the *N*-bromoamides **92**, **140a** and **140b**. This material was identified

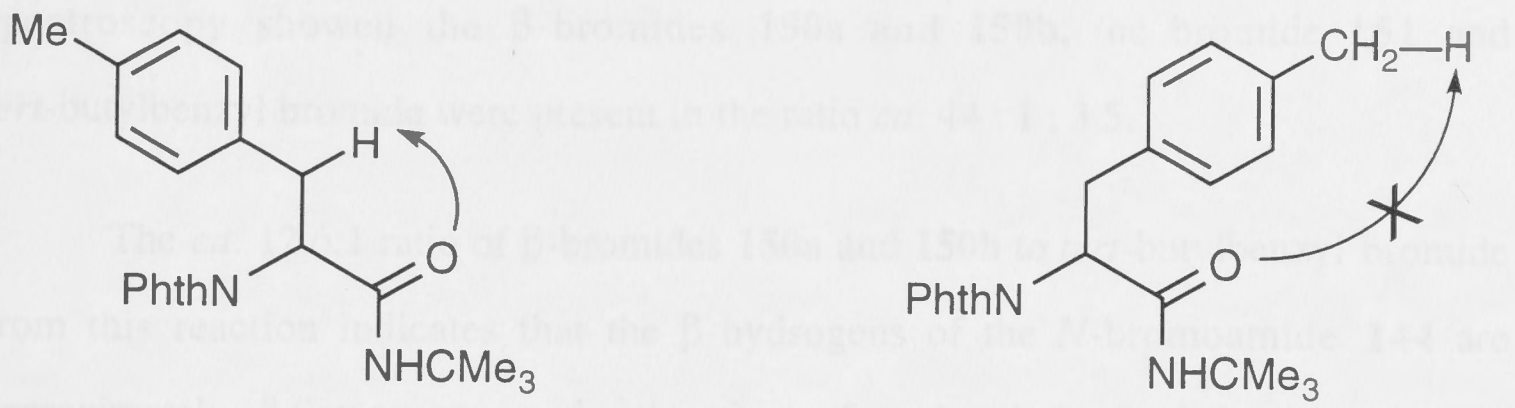
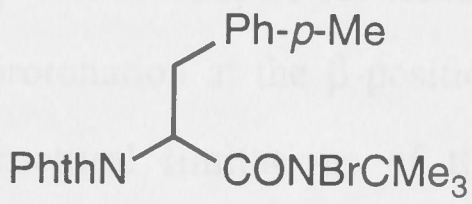


Figure 5.2. Spatial proximity of the amido group to the β- and *p*-methyl hydrogens of the *p*-methylphenylalanine derivative **94**.

from the ^{1}H NMR spectrum of the crude product, which contained a doublet of doublets resonance at δ 5.66 (*J* 5.0 and 10.8 Hz) corresponding to the α-hydrogen, consistent with that of the *N*-bromophenylalaninamide derivative **92**.



144

With the *N*-bromoamide **144** in hand, its photolysis reaction was investigated. The reaction was carried out in the presence of *tert*-butyltoluene in order to make a comparison between the reactivity of the non-activated benzylic hydrogens of *tert*-butyltoluene with that of the *p*-methyl hydrogens of the methylphenylalanine derivative **144**. Accordingly, a mixture of the *N*-bromoamide **144** (1.6 mM) and *tert*-butyltoluene, in the ratio *ca.* 1 : 1.4, was photolysed for 5 mins in carbon tetrachloride

at reflux under an atmosphere of nitrogen. Analysis of the crude product using ^{1}H NMR spectroscopy showed the β-bromides **150a** and **150b**, the bromide **151** and *tert*-butylbenzyl bromide were present in the ratio *ca.* 44 : 1 : 3.5.

The *ca.* 12.6:1 ratio of β-bromides **150a** and **150b** to *tert*-butylbenzyl bromide from this reaction indicates that the β-hydrogens of the *N*-bromoamide **144** are approximately 18 times more reactive than those of *tert*-butyltoluene, despite deactivation at the β-position of the *N*-bromoamide **144** due to stereoelectronic effects. Consistent with this result, the hydrogens at the β-position of the *N*-bromoamide **92** were determined to be between 12 and 26 times more reactive than those of *tert*-butyltoluene, based on the ratio of products of reaction of each substrate (Table 4.3) and allowing for the ratio of starting materials in the initial mixture.

The greater reactivity of the β-hydrogens of the *N*-bromoamide **144** compared to those of *tert*-butyltoluene is consistent with reaction of the *N*-bromoamide **144** *via* the mechanism proposed in the previous Chapter for reaction of the *N*-bromoamide **92** involving intramolecular deprotonation at the β-position by the basic amido group. Presumably, due to the structural limitations of the molecule, intramolecular deprotonation at the *p*-methyl substituent by the amido group cannot occur, and as a consequence, reaction at the β-position occurs to a much greater extent than at the *p*-methyl substituent.

In conclusion, through investigation of the reactions of the valine derivatives **95** and **96** and the *p*-methylphenylalanine derivatives **93** and **94**, it has been shown that the rates of reaction of the phenylalanine derived amides **19**, **78b** and **79b** with NBS are enhanced relative to those of the corresponding esters **17**, **78a** and **79a**, through stabilisation of the developing positive charge in the transition state by direct interaction of the amido group with the developing β-centred radicals. Furthermore, the regioselectivity of reaction of the *N*-bromo-*p*-methylphenylalanine derivative **144** has

provided convincing evidence in support of the mechanism proposed in Chapter 4 for reaction of the *N*-bromoamide **92** involving 1,4-neighbouring group participation by the amido moiety to deprotonate at the β-position.

CONCLUSION

The work described in this thesis has demonstrated the importance of neighbouring group participation in a variety of reactions. 1,4-Neighbouring group participation by an amido substituent has been discovered in hydrolysis reactions of *N*-phthaloyl-protected phenylalanine, nitrophenylalanine and valine derivatives, and has been shown to occur through stabilisation of electron deficient carbocation intermediates of reactions. The effect of the neighbouring group effect in these hydrolysis reactions was to enhance the rates of the substitution processes and influence the course of the reactions and the stereochemical outcome in some cases. In reactions of valine and nitrophenylalanine derivatives, elimination is the predominant reaction when the carboxy group is protected as an ester, whereas substitution dominates when the carboxy group is protected as an amide. The effect of the neighbouring group to promote substitution over elimination has been exploited in the synthesis of a derivative of naturally occurring β-hydroxyvaline and a β-hydroxynitrophenylalanine derivative, which is a precursor to chloramphenicol, and has the potential to be utilised in syntheses of a variety of substituted amino acid derivatives.

A procedure involving asymmetric *anti*-Markovnikov hydrobromination of a β,γ-dehydrovaline derivative has been developed for the stereoselective synthesis of a γ-hydroxyvaline diastereomer which could potentially be utilised in stereocontrolled syntheses of a variety of substituted amino acids.

1,4-Neighbouring group participation has been discovered in side chain radical bromination reactions of derivatives of phenylalanine, nitrophenylalanine and tyrosine, and has been shown to occur through direct stabilisation of positive charge at the β-position in the reaction transition states by the amido substituent. The rates of radical bromination of *N*-phthaloyl derivatives of phenylalanine, tyrosine and nitrophenylalanine are enhanced when the carboxy group was protected as an amide rather than as an ester,

which indicates that neighbouring group participation in radical reactions is of greater significance than previously recognised.

In summary, the various examples of neighbouring group participation by the protected carboxy group in the side chain reactions of amino acid derivatives discovered in the present work appear to be due to steric interactions between substituents within the molecules which move the carboxy oxygen in close proximity to the β-position, such that interaction with electron deficient centres of reactions can occur. These discoveries could be of great importance in the understanding of reactions of amino acids in peptides, such as in peptide secondary metabolism, in the auto-oxidation of amino acids and enzyme reaction mechanisms.

EXPERIMENTAL

General. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 or a Perkin Elmer 683 infrared spectrophotometer, calibrated against polystyrene film, as nujol mulls between sodium chloride plates unless stated otherwise. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a GEMINI 300 or a Bruker ACP-300 spectrophotometer, in deuterochloroform with tetramethylsilane (TMS) as the internal standard or in deuterium oxide (D_2O) using sodium [2,2,3,3-$^{2}H_4$]3-(trimethylsilyl)propionate (TSP) as an internal standard. Chemical shifts are quoted as δ in parts per million downfield from the internal standard. Multiplicities are abbreviated to: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; br, broad. Electron impact mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Microanalyses were performed by Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia or by the Microanalytical Services Unit of the Research School of Chemistry, Australian National University. Analytical thin layer chromatography was performed using Merck Keiselgel 60 F_{254} silica on aluminium backing plates. Silica chromatography was performed by positive pressure flash chromatography on Merck-Keiselgel 60 (230-400 mesh ASTM), using between 20-50% ethyl acetate in light petroleum (b.p. 66-68 °C) as eluant, unless otherwise stated. Alumina chromatography was performed on Merck basic aluminium oxide 90 (70-230 mesh ASTM). All solvents were distilled before use. Anhydrous diethyl ether was obtained by distillation from sodium benzophenone ketyl. Drying and purification of other reagents was performed using standard laboratory procedures.[212] Organic solutions were dried by the addition of anhydrous Na_2SO_4.

A Phillips MLU 300 W (220-240 V) sunlamp was used as the light source to initiate radical addition, bromination and reduction reactions, at a distance of between 5-10 cm from the reaction vessel. (*S*)-*O*-Acetyl-N^{α}-phthaloyltyrosine **136**,[59] (*S*)-*O*-acetyl-N^{α}-phthaloyltyrosine methyl ester **79**,[59] (2*S*,3*R*)-3-deutero-*N*-phthaloyl-phenylalanine methyl ester **26**,[58] (2*S*,3*S*)-3-deutero-*N*-phthaloylphenylalanine methyl ester **29**,[58] (2*S*,3*R*)-3-deutero-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **31b**,[58,59] (2*S*,3*S*)-3-deutero-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **31a**,[58,59] *N*-benzoyl-glycine methyl ester **7a**[213] and *N*-*tert*-butylbenzamide[214] were available for use. (*S*)-Valine, (*S*)-, (*R*)- and (*RS*)-*p*-nitrophenylalanine and (*RS*)-phenylalanine were purchased from Sigma chemical company.

(*S*)-*N*-Phthaloylvaline Methyl Ester 95

A mixture of *(S)*-valine (6.12 g, 52 mmol) and phthalic anhydride (7.74 g, 52 mmol) was heated for 40 mins at 150 °C. After cooling to room temperature, the resultant oil was dissolved in methanol (150 ml) then thionyl chloride (0.5 ml) was added dropwise. The solution was stirred overnight at room temperature, then was concentrated under reduced pressure. The residue was taken up in dichloromethane and the solution was washed twice with saturated sodium carbonate solution and then water. The solution was dried, then concentrated under reduced pressure, affording the title compound **95** as a colourless oil (11.28 g, 83%). δ_H 7.90-7.73 (m, 4 H, Phth), 4.58 (d, *J* 8.3 Hz, 1 H, α-H), 3.71 (s, 3 H, OMe), 2.77 (m, 1 H, β-H), 1.17 (d, *J* 6.7 Hz, 3 H, β-Me), 0.91 (d, *J* 6.8 Hz, 3 H, β'-Me); *m/z* (%) 261 ($M^{+\bullet}$, 10%), 202 (100), 187 (20); *m/z* 261.101 ($M^{+\bullet}$) [Calc. for $C_{14}H_{15}NO_4$ ($M^{+\bullet}$) *m/z* 261.100]. The spectral data for this material are consistent with literature values.[215]

(*R*)-3-Bromo-*N*-phthaloylvaline Methyl Ester 33

A mixture of *(S)-N*-phthaloylvaline methyl ester **95** (10.48 g, 40.2 mmol) and NBS (7.15 g, 40.2 mmol) was heated at reflux for 2 h in carbon tetrachloride (150 ml) while being irradiated with a 300 W sunlamp. The mixture was cooled in an ice bath, filtered, then washed twice with water. The solution was dried, then was concentrated and the resultant oil was crystallised from a mixture of ether, light petroleum and dichloromethane, to give the title compound **33** as a fine white crystalline solid (11.46 g, 84%), m.p. 133-135°C (Lit.[54] 129-131°C). δ_H 7.94-7.78 (m, 4 H, ArH), 5.16 (s, 1 H, α-H), 3.71 (s, 3 H, OMe), 2.15 (s, 3 H, β-Me), 1.99 (s, 3 H, β'-Me). The spectral data obtained for this compound are consistent with literature values.[54]

(*S*)-*N*-Phthaloyl-3,4-dehydrovaline Methyl Ester 38

Silver nitrate (8.19 g, 48 mmol) was added to a solution of the bromovaline derivative **33** (10.85 g, 32 mmol) in dry methanol (100 ml) over activated 4 Å sieves. The mixture was stirred at room temperature for 36 h in the dark, then saturated brine was added and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was partitioned between dichloromethane and water, and the organic layer was separated, dried and concentrated. Analysis of the crude product using ^{1}H-NMR spectroscopy showed the β,γ-alkene **38** and the corresponding α,β-alkene were present in the ratio *ca.* 5:1. A portion of this material was chromatographed on silica to give the alkene **38** as a colourless oil (3.46 g, 42%). δ_H 7.92-7.75 (m, 4 H), 5.38 (s, 1 H), 5.14 (s, 1 H), 5.11 (s, 1 H), 3.79 (s, 3 H, OMe), 1.92 (s, 3 H, β-Me). The ^{1}H NMR spectral data for this compound are consistent with that reported.[175,176]

(*S*)-4-Bromo-*N*-phthaloyl-3,4'-dehydrovaline Methyl Ester 39

To a solution of the alkene **38** (1.05 g, 4.1 mmol) in carbon tetrachloride (40 ml) under a nitrogen atmosphere was added NBS (0.76 g, 4.3 mmol) and the resultant mixture was heated at reflux for 2 h with irradiation from a 300 W sunlamp. The mixture was cooled, then filtered and the filtrate was washed with water and dried. The solution was then concentrated under reduced pressure and the crude product was chromatographed on silica, affording the title compound **39** as a yellow oil (1.09 g, 80%). ν_{max}(neat)/cm^{-1} 3492, 2952, 1776, 1722, 1614, 1470, 1438, 1382, 1340, 1304, 1256, 1212, 1108, 1088, 1028, 960, 912, 792, 720, 700, 668; δ_H 7.92-7.88 (m, 2 H, ArH), 7.80-7.76 (m, 2 H, ArH), 5.72 (s, 1 H), 5.62 (s, 1 H), 5.41 (s, 1 H), 4.28 (d, *J* 10.8 Hz, 1 H, γ-H), 4.13 (d, *J* 10.8 Hz, 1 H, γ'-H), 3.79 (s, 3 H, OMe); δ_C 167.2, 166.5, 137.9, 134.2, 131.3, 123.3, 121.2, 53.3, 52.6, 33.4; *m/z* (%) 339 ($M^{+\bullet}$, 20%),

337 ($M^{+\bullet}$, 20), 280 (20), 278 (20), 258 (100), 218 (20), 202 (30), 200 (40), 199 (30), 198 (30), 160 (30), 130 (40), 104 (65); *m/z* 336.996 ($M^{+\bullet}$) [Calc. for $C_{14}H_{12}NO_4{}^{79}Br$ ($M^{+\bullet}$) *m/z* 336.995].

(*S*)-4-Hydroxy-*N*-phthaloyl-3,4'-dehydrovaline Methyl Ester 40

To a solution of (*S*)-4-bromo-*N*-phthaloyl-3,4'-dehydrovaline methyl ester **39** (120 mg, 0.4 mmol) in acetone (10 ml) was added a solution of silver nitrate (124 mg, 0.7 mmol) in water (10 ml) and the resultant mixture was stirred at room temperature for 16 h. Saturated brine was added and the mixture was then filtered and the filtrate was concentrated under reduced pressure. The crude product was analysed using ^{1}H NMR spectroscopy, which showed (*S*)-4-hydroxy-*N*-phthaloyl-3,4'-dehydrovaline methyl ester **40** as the major product from the reaction. ν_{max}(neat)/cm^{-1} 3500, 3020, 2960, 2920, 2775, 1750, 1720, 1640, 1470, 1430, 1380, 1340, 1220, 1110, 1090, 1030, 920, 760, 720, 670; δ_H 7.91-7.86 (m, 2 H, ArH), 7.79-7.73 (m, 2 H, ArH), 5.61 (s, 1 H), 5.44 (s, 1 H), 5.30 (s, 1 H), 4.38-4.20 (m, 2 H, CH_2), 3.78 (s, 3 H, OMe), 2.62 (br s, 1 H, OH); δ_C 168.3, 167.3, 141.9, 134.3, 131.5, 123.6, 118.0, 64.2, 53.7, 52.9; *m/z* (%) 274 (M-H, 35%), 243 (100), 216 (53), 199 (33), 160 (15), 130 (43); *m/z* 274.072 (M-H) [Calc. for $C_{14}H_{12}NO_5$ (M-H) *m/z* 274.072]. Purification of this material was attempted using chromatography on silica, however, the lactone **99** was the sole product isolated. ν_{max}(neat)/cm^{-1} 3020, 2930, 1790, 1780, 1760, 1740, 1680, 1610, 1470, 1450, 1410, 1380, 1340, 1300, 1215, 1150, 1130, 1080, 1050, 1000, 880, 750, 680; δ_H 7.98-7.93 (m, 2 H, ArH), 7.83-7.79 (m, 2 H, ArH), 4.95 (s, 2 H, CH_2), 2.13 (s, 3 H, Me); δ_C 165.5, 160.7, 134.6, 131.8, 124.0, 119.1, 110.7, 71.8, 29.2; *m/z* (%) 243 ($M^{+\bullet}$, 100%), 214 (17), 198 (19), 186 (61), 132 (30), 104 (87), 76 (57). Further attempts to purify this material using chromatography on silica with 1% and then 5% triethylamine in the eluant were unsuccessful, with only the lactone **99** isolated. Neither the alcohol **40** nor the lactone **41** were detected following

chromatography. Attempted purification using chromatography on basic alumina resulted in decomposition and neither the alcohol **40** nor the lactones **41** and **99** were isolated.

(*R*)-3,4-Dibromo-*N*-phthaloylvaline Methyl Ester 43

To a solution of (*S*)-*N*-phthaloyl-3,4-dehydrovaline methyl ester **38** (119 mg, 0.46 mmol) in carbon tetrachloride (40 ml) was added a solution of bromine in carbon tetrachloride (6 ml, 0.13 M). The solution was stirred at room temperature for 16 h, then was concentrated under reduced pressure. The crude product was analysed using ^{1}H NMR spectroscopy, which showed a *ca.* 3:1 mixture of diastereomers of (*R*)-3,4-dibromo-*N*-phthaloylvaline methyl ester **43**. (major diastereomer) δ_H 7.95-7.78 (m, 4 H, ArH), 5.49 (s, 1 H, α-H), 4.73 (d, *J* 10.7 Hz, 1 H, γ-H), 3.91 (d, *J* 10.7 Hz, 1 H, γ'-H), 3.75 (s, 3 H, OMe), 2.02 (s, 3 H, Me); (minor isomer) δ_H 7.95-7.78 (m, 4 H, ArH), 5.61 (s, 1 H, α-H), 4.63 (d, *J* 10.7 Hz, 1 H, γ-H), 3.98 (d, *J* 10.7 Hz, 1 H, γ'-H), 3.71 (s, 3 H, OMe), 2.13 (s, 3 H, Me); *m/z* (%) 422 (MH, 10%), 420 (MH, 20), 418 (MH, 10), 362 (10), 360 (20), 358 (10), 340 (80), 338 (80), 308 (20), 306 (20), 280 (80), 278 (80), 250 (68), 248 (75), 218 (100), 200 (100), 190 (65), 130 (75), 104 (80); *m/z* 416.922 ($M^{+\bullet}$) [Calc. for $C_{14}H_{13}NO_4{}^{79}Br_2$ ($M^{+\bullet}$) *m/z* 416.921]. This material was unstable and was therefore used without purification or further characterisation.

Treatment of the Dibromide 43 with Tri-*n*-butyltin Hydride.

To a solution of the crude dibromide **43** (189 mg, 0.45 mmol) in benzene (10 ml) was added tributyltin hydride (120 μl, 0.45 mmol) and a catalytic amount of AIBN. The solution was stirred for 16 h at room temperature, then concentrated and the residue was taken up in ether (20 ml). The ether solution was washed twice with aqueous saturated potassium fluoride solution, then filtered and the solution was concentrated under reduced pressure. Analysis of the crude product using ^{1}H NMR spectroscopy showed that the dibromide **43** had reacted to give the alkene **38**. There were no peaks in the ^{1}H NMR spectrum that could be attributed to the γ-bromide diastereomers **44a** and **44b**.

Treatment of (*S*)-*N*-Phthaloyl-3,4-dehydrovaline Methyl Ester 38 with Chlorine in Carbon Tetrachloride

To a solution of the β,γ-alkene **38** (79 mg, 0.3 mmol) in carbon tetrachloride (10 ml) was added a solution of chlorine in carbon tetrachloride (0.4 ml, 2.4 M). The solution was stirred for 16 h at room temperature, then was concentrated under reduced pressure. The crude product was chromatographed on silica affording (*S*)-4-chloro-*N*-phthaloyl-3,4'-dehydrovaline methyl ester **103** as a colourless oil (48 mg, 54%). ν_{max}(neat)/cm^{-1} 3040, 2960, 1780, 1750, 1720, 1620, 1475, 1440, 1390, 1340, 1300, 1230, 1120, 1095, 1030 and 920; δ_H 7.98-7.75 (m, 4 H, ArH), 5.68 (s, 1 H), 5.59 (s, 1 H), 5.42 (s, 1 H), 4.37 (d, *J* 12.1 Hz, 1 H, γ-H), 4.22 (d, *J* 12.1 Hz, 1 H, γ'-H), 3.80 (s, 3 H, OMe); *m/z* (%) 295 ($M^{+\bullet}$, 1%), 293 ($M^{+\bullet}$, 3), 258 (100), 236 (10), 234 (25), 200 (10), 199 (10), 198 (10), 160 (20), 130 (20), 104 (25); *m/z* 258.078 (M-Cl) [Calc. for $C_{14}H_{12}NO_4$ (M-Cl) *m/z* 258.077]; (Found: C, 57.2; H, 4.2; N, 4.7. Calc. for $C_{14}H_{12}NO_4Cl$: C, 57.2; H, 4.1; N, 4.8%).

Treatment of (*S*)-*N*-Phthaloyl-3,4-dehydrovaline Methyl Ester 38 with Chlorine in the Presence of a Radical Inhibitor.

The alkene **38** was treated with a solution of chlorine in carbon tetrachloride using the procedure described above for the preparation of the chloride **103** except that hydroquinone was added and the reaction was stirred for 16 h in the dark. The solution was concentrated under reduced pressure then the crude material was analysed using ^{1}H NMR spectroscopy. This material was identical to that produced in the reaction described above for the reaction of the alkene **38** with chlorine.

(2*S*,3*S*)-4-Bromo-*N*-phthaloylvaline Methyl Ester 44a and (2*S*,3*R*)-4-Bromo-*N*-phthaloylvaline Methyl Ester 44b

Through a solution of the β,γ-dehydrovaline derivative **38** (819 mg, 3.2 mmol) in carbon tetrachloride (50 ml), in an ice-water bath, was passed a dry stream of hydrogen bromide, for 5 mins. During this time, and for a further 40 mins, the solution was irradiated with a 300 W sunlamp. The resultant solution was washed twice with water, then it was dried and concentrated under reduced pressure to afford a crude product as a colourless oil. Analysis of this material using ^{1}H NMR spectroscopy, showed a 2.2:1 mixture of the bromides **44a** and **44b** (944 mg, 88%). **44a** δ_H 7.94-7.78 (m, 4 H, ArH), 5.02 (d, *J* 8.4 Hz, 1 H, α-H), 3.90 (dd, *J* 5.1, 10.2 Hz, 1 H, γ-H), 3.66 (dd, *J* 3.9, 10.2 Hz, 1 H, γ'-H), 3.73 (s, 3 H, OMe), 3.01 (m, 1 H, β-H), 1.03 (d, *J* 6.9 Hz, 3 H, β-Me); δ_C 168.2, 167.3, 134.2, 131.4, 123.5, 53.9, 52.5, 38.7, 34.8, 15.9; **44b** δ_H 7.94-7.78 (m, 4 H, ArH), 4.91 (d, *J* 7.4 Hz, 1 H, α-H), 3.74 (s, 3 H, OMe), 3.65 (dd, *J* 3.7, 10.3 Hz, 1 H, γ-H), 3.25 (dd, *J* 6.8, 10.3 Hz, 1 H, γ'-H), 3.01 (m, 1 H, β-H), 1.30 (d, *J* 6.6 Hz, 3 H, β-Me); δ_C 168.5, 167.2, 134.0, 131.3, 123.7, 54.7, 52.3, 36.9, 35.3, 16.7; *m/z* (%) 341 ($M^{+\bullet}$, 1%), 339 ($M^{+\bullet}$, 1), 281 (20), 279 (20), 219 (50), 201 (100), 199 (100); *m/z* 339.009 ($M^{+\bullet}$) [Calc. for $C_{14}H_{14}{}^{79}BrNO_4$ ($M^{+\bullet}$) *m/z* 339.016].

(2*S*,3*S*)-4-Iodo-*N*-phthaloylvaline Methyl Ester 107a and (2*S*,3*R*)-4-Iodo-*N*-phthaloylvaline Methyl Ester 107b

A solution of a 2.2:1 mixture of the bromides **44a** and **44b** (944 mg, 2.8 mmol) and sodium iodide (1.28 g, 8.5 mmol) in acetone (40 ml) was heated at reflux for 2 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the solution was washed with aqueous sodium metabisulfite solution, then water, and then it was dried and concentrated under reduced pressure, to give a 2.2:1 mixture of the iodides **107a** and **107b** as a yellow oil. **107a** δ_H 7.97-7.76 (m, 4 H, ArH), 4.89 (d, *J* 8.3 Hz, 1 H, α-H), 3.74 (s, 3 H, OMe), 3.63 (dd, *J* 5.4, 10.2 Hz, 1 H, γ-H), 3.50 (dd, *J* 3.9, 10.2 Hz, 1 H, γ'-H), 2.59 (m, 1 H, β-H), 0.99 (d, *J* 6.7 Hz, 3 H, β-Me); **107b** δ_H 7.97-7.76 (m, 4 H, ArH), 4.83 (d, *J* 7.3 Hz, 1 H, α-H), 3.74 (s, 3 H, OMe), 3.47 (dd, *J* 3.8, 10.2 Hz, 1 H, γ-H), 3.01 (dd, *J* 7.8, 10.2 Hz, 1 H, γ'-H), 2.79 (m, 1 H, β-H), 1.25 (d, *J* 6.5 Hz, 3 H, β-Me). The unstable iodides **107a** and **107b** were not purified and were used in the following reaction without further characterisation.

(2*S*,3*S*)-4-Hydroxyvaline 3a

To a stirred solution of the crude iodides **107a** and **107b** in aqueous acetone (30 ml) was added silver nitrate (711 mg, 4.2 mmol). The mixture was stirred at room temperature in darkness for 60 h, then brine was added. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the resultant solution was washed with brine, then dried and concentrated under reduced pressure. The crude product was analysed using ^{1}H NMR spectroscopy, which showed a mixture of the (2*S*,3*S*)-lactone **42a** and the alcohols **36a** and **36b**. **42a** δ_H 7.92-7.78 (m, 4 H, ArH), 4.70 (d, *J* 11.5 Hz, 1 H, α-H), 4.66

(dd, *J* 8.4, 10.3 Hz, 1 H, γ-H), 3.98 (dd, *J* 9.2, 10.3 Hz, 1 H, γ'-H), 3.27-3.11 (m, 1 H, β-H), 1.23 (d, *J* 6.6 Hz, 3 H, Me); **36a** δ_H 7.93-7.72 (m, 4 H, ArH), 5.05 (d, *J* 5.4 Hz, 1 H, α-H), 3.74 (s, 3 H, OMe), 3.68 (dd, *J* 4.8, 11.8 Hz, 1 H, γ-H), 3.39 (dd, *J* 8.3, 11.8 Hz, 1 H, γ'-H), 2.82 (m, 1 H, β-H), 0.93 (d, *J* 6.6 Hz, 3 H, β-Me); **36b** δ_H 7.93-7.72 (m, 4 H, ArH), 4.91 (d, *J* 6.3 Hz, 1 H, α-H), 3.75 (s, 3 H, OMe), 3.57 (dd, *J* 5.0, 12.0 Hz, 1 H, γ-H), 3.51 (dd, *J* 6.6, 12.0 Hz, 1 H, γ'-H), 2.79 (m, 1 H, β-H), 1.10 (d, *J* 7.2 Hz, 3 H, β-Me).

The mixture containing the lactone **42a** and alcohols **36a** and **36b** dissolved in a 2:1 mixture of 6 N hydrochloric and glacial acetic acid (25 ml), and the solution was heated at reflux for 4 h. After cooling to room temperature, the solution was concentrated under reduced pressure, and the residue was taken up in water and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in water, then the solution was applied to a column of Amberlite IR 120 cation exchange resin (NH_4^+ form). The column was washed with water (1 L), then eluted with aqueous ammonia solution (1 L). The eluate was boiled until no ammonia could be detected, then concentrated under reduced pressure affording a 3:1 mixture of the diastereomers **3a** and **3b** (223 mg, 60%). **3a** δ_H (D_2O) 3.85 (d, *J* 3.2 Hz, 1 H, α-H), 3.69 (dd, *J* 5.2, 11.4 Hz, 1 H, γ-H), 3.57 (dd, *J* 6.9, 11.4 Hz, 1 H, γ'-H), 2.33 (m, 1 H, β-H), 0.94 (d, *J* 7.2 Hz, 3 H, Me); **3b** δ_H (D_2O) 3.74 (d, *J* 4.4 Hz, 1 H, α-H), 3.64 (d, *J* 5.6 Hz, 2 H, CH_2O), 2.17 (m, 1 H, β-H), 1.02 (d, *J* 7.0 Hz, 3 H, Me). Fractional crystallisation of this mixture from acetone and water afforded the (2*S*,3*S*)-isomer **3a** (94 mg, 25%), m.p. 219-221 °C (dec.) (Lit.[22] 212-214 °C (dec.)); δ_C (D_2O) 176.9, 67.0, 60.2, 38.4, 13.5; $[\alpha]_{365}^{24}$ +24.0° (c, 0.2 in H_2O) (Lit.[22] (2*S*,3*S*)-isomer **3a** +23.3°; (2*S*,3*R*)-isomer **3b** +26.4°); (Found: C, 45.0; H, 8.4; N, 10.5. Calc for $C_5H_{11}NO_3$: C, 45.1; H, 8.3; N, 10.5%).

(3*S*,4*S*)-4-Methyl-3-phthalimido-γ-butyrolactone 42a and (3*S*,4*R*)-4-Methyl-3-phthalimido-γ-butyrolactone 42b

The title compounds **42a** and **42b** were synthesised from a mixture of the iodides **107a** and **107b** by treatment with aqueous silver nitrate, using the procedure described above. In this case, however, the crude mixture was chromatographed on silica affording a *ca.* 6:1 mixture of the lactone diastereomers **42a** and **42b** as a colourless oil (607 mg, 67% from the bromides **44a** and **44b**). ν_{max}(neat)/cm^{-1} 3490, 2970, 1770, 1720, 1620, 1470, 1390, 1340, 1200, 1010; (3*S*,4*R*)-diastereomer **42b** δ_H 7.92-7.78 (m, 4 H, ArH), 5.01 (d, *J* 10.0 Hz, 1 H, α-H), 4.66 (dd, *J* 8.4, 8.7 Hz, 1 H, γ-H), 4.26 (dd, *J* 8.0, 8.7 Hz, 1 H, γ'-H), 3.06-2.90 (m, 1 H, β-H), 1.02 (d, *J* 7.1 Hz, 3 H, Me); *m/z* (%) 245 ($M^{+\bullet}$, 5%), 201 (25), 186 (100); *m/z* 245.070 ($M^{+\bullet}$) [Calc. for $C_{13}H_{11}NO_4$ ($M^{+\bullet}$) *m/z* 245.069]; (Found: C, 63.5; H, 5.0; N, 5.4. Calc. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N 5.7%). The ^{1}H NMR spectral data for the (3*S*,4*S*)-lactone **42a** is given above.

Extraction of γ-Hydroxyvaline from *Kalanchoe daigremontiana*

The leaves and stems of *Kalanchoe daigremontiana* were freeze-dried (20 g dry weight) and the residue was partitioned between chloroform and water. The mixture was separated and the aqueous phase was washed with chloroform. The solution was acidified to pH 1 with concentrated hydrochloric acid then stirred for 16 h at room temperature, then was filtered and the filtrate was concentrated to afford a crude extract. The crude extract was dissolved in water, then chromatographed on Amberlite IR 120 ion exchange resin using the procedure outlined by Pollard *et al.*[82] to afford the natural product which was then recrystallised from acetone and water (43 mg, 0.2%), m.p. 208-214 °C (Lit.[22] 212-214 °C). $[\alpha]_{365}^{20}$ +22.0° (c, 0.44 in H_2O) (Lit.[22] (2*S*,3*S*)-isomer **3a** +23.3°; (2*S*,3*R*)-isomer **3b** +26.4°). The ^{1}H NMR spectral data for this material are

identical to those given above for the synthesised (2*S*,3*S*)-isomer **3a**. The relative stereochemistry of this material was confirmed through X-ray crystallographic analysis (Appendix 4).

N-Phthaloylphenylalanine 108

A mixture of phenylalanine (11.23 g, 68.0 mmol) and finely ground phthalic anhydride (10.06 g, 68.0 mmol) was heated at 150 °C for 40 mins. The resultant yellow gum was taken up in dichloromethane then washed with water and dried, then concentrated under reduced pressure, affording the title compound **108** as a white crystalline solid (17.98 g, 90%), m.p. 177-178 °C (Lit.[216] 178 °C). δ_H 10.68 (br s, 1 H, CO_2H), 7.80-7.74 (m, 2 H, ArH), 7.71-7.66 (m, 2 H, ArH), 7.23-7.10 (m, 5 H, Ph), 5.23 (t, *J* 8.5 Hz, 1 H, α-H), 3.59 (d, *J* 8.5 Hz, 2 H, β-H). The spectral data for this material are consistent with that previously reported.[59]

N-Phthaloylphenylalanine Methyl Ester 17

The title compound **17** was prepared as described above for the preparation of the valine derivative **95**, by treatment of *N*-phthaloylphenylalanine **108** (6.13 g, 20.8 mmol) with methanol which had been treated with thionyl chloride, and isolated as a colourless crystalline solid (5.79 g, 90%), m.p. 89-91 °C (Lit.[174] 73-75 °C). δ_H 7.79-7.75 (m, 2 H, ArH), 7.71-7.66 (m, 2 H, ArH), 7.22-7.12 (m, 5 H, Ph), 5.16 (dd, *J* 5.5, 11.0 Hz, 1 H, α-H), 3.78 (s, 3 H, OMe), 3.62 (dd, *J* 5.5, 14.4 Hz, 1 H, β-H), 3.54 (dd, *J* 11.0, 14.4 Hz, 1 H, β'-H). The spectral data for this material are consistent with those previously reported.[59]

N-*tert*-Butyl-N^{α}-phthaloylphenylalaninamide 19

To a suspension of *N*-phthaloylphenylalanine **108** (619 mg, 2.1 mmol) in dichloromethane (10 ml) was added triethylamine (0.29 ml, 2.1 mmol). The resultant solution was cooled to 0 °C, then ethyl chloroformate (0.20 ml, 2.1 mmol) was added. That mixture was stirred for 10 min, then *tert*-butylamine (0.22 ml, 2.1 mmol) was added and the solution was warmed to room temperature. After stirring for a further 30 min, the mixture was filtered and the filtrate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water, then it was dried and concentrated under reduced pressure. The residue was chromatographed to give the title compound **19**, as a colourless crystalline solid after recrystallisation from a mixture of ethyl acetate and light petroleum (392 mg, 53%), 192-194 °C (Lit.[59] 194-195 °C). δ_H 7.80-7.66 (m, 4 H, ArH), 7.17 (m, 5 H, Ph), 5.86 (br s, 1 H, NH), 4.98 (dd, *J* 6.7, 10.0 Hz, 1 H, α-H), 3.56 (dd, *J* 6.7, 14.1 Hz, 1 H, β-H), 3.47 (dd, *J* 10.0, 14.1 Hz, 1 H, β'-H), 1.30 (s, 9 H, CMe_3). The spectral data for this compound are consistent with those reported.[59]

(2*RS*,3*RS*)-3-Bromo-*N*-phthaloylphenylalanine Methyl Ester 18b and (2*RS*,3*SR*)-3-Bromo-*N*-phthaloylphenylalanine Methyl Ester 18a

A mixture of *N*-phthaloylphenylalanine methyl ester **17** (4.66 g, 15.1 mmol) and NBS (2.68 g, 15.1 mmol) in carbon tetrachloride (100 ml) was heated at reflux for 2 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature, then filtered and the filtrate was washed with water, then dried. Concentration of the resultant solution afforded the title compounds **18a** and **18b** as a 1:1 mixture (5.80 g, 99%). **18b** δ_H 7.97-7.94 (m, 2 H, ArH), 7.82-7.78 (m, 2 H, ArH), 7.59 (m, 2 H, Ph), 7.43-7.33 (m, 3 H, Ph), 6.02 (d, *J* 11.2 Hz, 1 H, β-H), 5.52 (d, *J* 11.2 Hz, 1 H, α-H), 3.55 (s, 3 H, OMe); **18a** δ_H 7.72-7.62 (m, 6 H,

ArH and Ph), 7.23-7.13 (m, 3 H, Ph), 5.91 (d, *J* 10.5 Hz, 1 H, β-H), 5.59 (d, *J* 10.5 Hz, 1 H, α-H), 3.82 (s, 3 H, OMe). The ^{1}H NMR spectral data for this material were consistent with literature values.[54]

(2*RS*,3*RS*)-3-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide 20b and (2*RS*,3*SR*)-3-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide 20a

The title compounds **20a** and **20b** were prepared as a 1:1 mixture of diastereomers from *N*-*tert*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide **19** by treatment with NBS, as described above for the preparation of the bromoesters **18a** and **18b**, and isolated in quantitative yield. **20b** δ_H 7.96-7.77 (m, 4 H, ArH), 7.62-7.34 (m, 5 H, Ph), 6.17 (d, *J* 11.8 Hz, 1 H, β-H), 5.76 (br s, 1 H, NH), 5.22 (d, *J* 11.8 Hz, 1 H, α-H), 1.02 (s, 9 H, CMe_3); **20a** δ_H 7.72-7.62 (m, 4 H, ArH), 7.38-7.11 (m, 5 H, Ph), 6.41 (br s, 1 H, NH), 6.05 (d, *J* 11.4 Hz, 1 H, β-H), 5.32 (d, *J* 11.4 Hz, 1 H, α-H), 1.40 (s, 9 H, CMe_3). The ^{1}H NMR spectral data for these materials were consistent with literature values.[53,59,96]

(*S*)-*N*-*tert*-Butyl-*N*$^{\alpha}$-phthaloylvalinamide 96

To a suspension of *(S)*-*N*-phthaloylvaline **97** (15.57 g, 63 mmol) in dichloromethane (60 ml) was added triethylamine (6.37 g, 63 mmol). The resulting solution was cooled to 0 °C, then ethyl chloroformate (6.87 g, 63 mmol) was added and the mixture was stirred for 15 min. *tert*-Butylamine (4.60 g, 63 mmol) was added and the mixture was allowed to warm to room temperature and was stirred for a further 40 min. The mixture was filtered and the filtrate was washed with water, then it was dried and concentrated under reduced pressure. A portion (*ca.* 4.6 g, 25%) of the residue was chromatographed, to give the title compound **96** as a colourless crystalline solid (2.60 g),

m.p. 144-147 °C; $[\alpha]_D^{21}$ +32.3° (c, 8.7 in $CHCl_3$); ν_{max}/cm^{-1} 3400, 3365, 2920, 2850, 1760, 1710, 1680, 1550, 1530, 1470, 1400, 1070, 715; δ_H 7.91-7.81 (m, 4 H, Phth), 7.13 (br s, 1 H, NH), 4.35 (d, *J* 11.3 Hz, 1 H, α-H), 2.88 (m, 1 H, β-H), 1.39 (s, 9 H, CMe_3), 1.15 (d, *J* 6.7 Hz, 3 H, Me), 0.87 (d, *J* 6.5 Hz, 3 H, Me'); δ_C 170.5, 169.9, 136.3, 133.4, 125.6, 66.7, 53.3, 30.6, 29.8, 21.7, 21.6; *m/z* (%) 303 ($M+H^+$, 1%), 275 (1), 260 (5), 202 (100); (Found: C, 67.3; H, 7.6; N, 9.2%. Calc. for $C_{17}H_{22}N_2O_3$: C, 67.5; H, 7.3; N, 9.3%).

(*R*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylvalinamide 73

A mixture of NBS (1.18 g, 6.6 mmol) and the valinamide **96** (1.33 g, 4.4 mmol) in carbon tetrachloride (60 ml) was heated at reflux for 2 h, whilst being irradiated with a 300 W sunlamp, then was cooled to and filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give the title compound **73** as fine colourless needles, after recrystallisation from a mixture of light petroleum and ether (1.54 g, 92%), m.p. 139-141 °C; $[\alpha]_D^{20}$ +11.6° (c, 3.03 in $CHCl_3$); ν_{max}/cm^{-1} 3380, 2920, 2850, 1710, 1530, 1460, 1380, 1080, 720; δ_H 7.67 (m, 4 H, Phth), 5.28 (s, 1 H, α-H), 2.07 (s, 3 H, Me), 1.86 (s, 3 H, Me'), 1.30 (s, 9 H, CMe_3); δ_C 168.0, 163.8, 134.4, 131.2, 123.7, 65.9, 65.6, 51.9, 33.3, 32.8 and 28.4; *m/z* (%) 383 (MH, 5%), 382 (M, 7), 381 (MH and M–H, 10), 380 (M, 7), 379 (M–H, 5), 367 (15), 365 (15), 327 (30), 325 (30), 310 (30), 308 (30), 301 (100), 282 (100), 280 (100); (Found: C, 53.7; H, 5.5; N, 7.1. Calc. for $C_{17}H_{21}BrN_2O_3$: C, 53.6; H, 5.6; N, 7.3%).

(*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine 110

A mixture of (*R*)-*p*-nitrophenylalanine **109** monohydrate (1.78 g, 7.81 mmol), phthalic anhydride (1.27 g, 8.58 mmol) and triethylamine (1.1 ml, 7.95 mmol) was heated at reflux in toluene (60 ml) for 3 h, during which time water was continuously removed using a Dean-Stark apparatus. The resultant mixture was cooled in an ice bath and then it was concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with dilute aqueous hydrochloric acid and water, then was dried and concentrated under reduced pressure. Crystallisation of the solid residue from a mixture of ethyl acetate and light petroleum yielded the title compound **110** as a pale yellow crystalline solid (2.57 g, 97%), m.p. 203-207 °C; $[\alpha]_{578}^{25}$ +234.5° (c, 0.31 in MeOH); δ_H 8.09 (d, *J* 8.7 Hz, 2 H, ArH), 7.83-7.72 (m, 4 H, Phth), 7.36 (d, *J* 8.7 Hz, 2 H, ArH), 5.26 (dd, *J* 7.3, 9.2 Hz, 1 H, α-H), 3.72 (m, 2 H, β-H).

(*RS*)-*N*-Phthaloyl-*p*-nitrophenylalanine

This compound was prepared from (*RS*)-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding (*R*)-isomer **110**, and obtained in 93% yield, m.p. 185-187 °C.

(*S*)-*N*-Phthaloyl-*p*-nitrophenylalanine

This compound was prepared from (*S*)-*p*-nitrophenylalanine monohydrate, as described above for the synthesis of the corresponding (*R*)-enantiomer **110**, and obtained in 57% yield, m.p. 200-202 °C (Lit.[217] 204.7 °C); $[\alpha]_{578}^{19}$ –230.2° (c, 0.086 in MeOH) (Lit.[217] –232.5° (c, 1.55 in MeOH)).

(*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine Methyl Ester 78a

(*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine **110** (2.50 g, 7.35 mmol) was dissolved in dry methanol (50 ml) which had been pretreated with thionyl chloride (400 mg, 3.36 mmol). The solution was stirred under anhydrous conditions for 16 h, then it was concentrated under reduced pressure. The residue was dissolved in dichloromethane, and the solution was washed with aqueous sodium carbonate and water, then dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the title compound **78a** as a colourless solid (2.24 g, 86%), m.p. 121-122 °C; ν_{max}/cm^{-1} 1775, 1750, 1715, 1600, 1520, 1390, 1345, 1240, 860, 720; δ_H 8.06 (d, *J* 8.6 Hz, 2 H, ArH), 7.82-7.72 (m, 4 H, Phth), 7.45 (d, *J* 8.6 Hz, 2 H, ArH), 5.31 (dd, *J* 5.5, 10.9 Hz, 1 H, α-H), 3.81 (s, 3 H, OMe), 3.77 (dd, *J* 5.5, 14.3 Hz, 1 H, β-H), 3.71 (dd, *J* 10.9, 14.3 Hz, 1 H, β'-H); *m/z* (%) 354 ($M^{+\bullet}$, 12%), 295 (37), 278 (14), 218 (36), 207 (100), 190 (37), 176 (25), 130 (33), 104 (17), 76 (21).

(2*S*,3*S*)-3-Bromo-*N*-phthaloyl-*p*-nitrophenylalanine Methyl Ester 71a and (2*S*,3*R*)-3-Bromo-*N*-phthaloyl-*p*-nitrophenylalanine Methyl Ester 71b

To a solution of (*R*)-*N*-phthaloyl-*p*-nitrophenylalanine methyl ester **78a** (2.20 g, 6.21 mmol) in carbon tetrachloride (40 ml), NBS (1.20 g, 6.74 mmol) was added and the mixture was heated at reflux for 4 h, whilst being irradiated with a 300 W sunlamp. The mixture was then allowed to cool, then it was filtered. The filtrate was washed with water, then dried and concentrated under reduced pressure, to give a 1:1 mixture of the title compounds **71a** and **71b** as a colourless solid (2.69 g, 100%). Fractional recrystallisation of the mixture from a combination of dichloromethane and light petroleum gave the (2*S*,3*S*)-bromide **71a** (1.17 g, 43%), m.p. 198-201 °C; ν_{max}/cm^{-1} 1775, 1750, 1720, 1600, 1525, 1340, 1215, 1100, 820, 715; δ_H 8.27 (d, *J* 8.8 Hz,

2 H, ArH), 7.99-7.82 (m, 4 H, Phth), 7.78 (d, *J* 8.8 Hz, 2 H, ArH), 6.02 (d, *J* 11.2 Hz, 1 H, β-H), 5.51 (d, *J* 11.2 Hz, 1 H, α-H), 3.59 (s, 3 H, OMe); *m/z* (%) 434 ($M^{+\bullet}$, 2%), 432 ($M^{+\bullet}$, 2), 375 (6), 373 (6), 353 (4), 352 (9), 321 (6), 294 (29), 293 (17), 287 (10), 285 (10), 247 (7), 219 (16), 218 (100), 190 (30), 130 (18), 104 (40), 76 (37); (Found: C, 49.8; H, 3.0; N, 6.5. Calc. for $C_{18}H_{13}BrN_2O_6$: C, 49.9; H, 3.0; N, 6.5%). Further recrystallisation gave the (2*S*,3*R*)-bromide **71b** (1.07 g, 40%), m.p. 195-197 °C; ν_{max}/cm^{-1} 1775, 1755, 1720, 1605, 1525, 1390, 1350, 855, 720; δ_H 8.07 (d, *J* 8.7 Hz, 2 H, ArH), 7.76-7.68 (m, 4 H, Phth), 7.56 (d, *J* 8.7 Hz, 2 H, ArH), 5.97 (d, *J* 10.3 Hz, 1 H, β-H), 5.59 (d, *J* 10.3 Hz, 1 H, α-H), 3.83 (s, 3 H, OMe); *m/z* (%) 434 ($M^{+\bullet}$, 1%), 432 ($M^{+\bullet}$, 1), 375 (3), 373 (3), 353 (6), 352 (3), 321 (7), 294 (20), 293 (12), 287 (3), 285 (3), 247 (5), 219 (15), 218 (100), 190 (29), 130 (16), 104 (28), 76 (26); (Found: C, 49.8; H, 3.0; N, 6.6. Calc. for $C_{18}H_{13}BrN_2O_6$: C, 49.9; H, 3.0; N, 6.5%). The structure of the bromide **71b** was confirmed through X-ray crystallographic analysis (Appendix 5).

(*RS*)-*N*-*tert*-Butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide

To a suspension of (*RS*)-*N*-phthaloyl-*p*-nitrophenylalanine (2.00 g, 5.88 mmol) in dichloromethane (40 ml), triethylamine (0.81 ml, 5.85 mmol) was added. The resultant solution was cooled to 0 °C, then ethyl chloroformate (0.56 ml, 5.86 mmol) was added. That mixture was stirred for 10 min, then *tert*-butylamine (0.61 ml, 5.85 mmol) was added and the solution was warmed to room temperature. After stirring for a further 30 min, the mixture was filtered and the filtrate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water, then it was dried and concentrated under reduced pressure. The residue was chromatographed to give the title compound, as a colourless crystalline solid after recrystallisation from a mixture of ethyl acetate and light petroleum (1.26 g, 54%), m.p. 215-216 °C. ν_{max}/cm^{-1} 3316, 2920, 2848, 1774, 1714, 1658, 1554, 1516, 1456, 1382, 1344, 1220, 1088, 1016, 888, 874,

766, 726; δ_H 8.03 (d, *J* 8.6 Hz, 2 H, ArH), 7.77-7.69 (m, 4 H, Phth), 7.33 (d, *J* 8.6 Hz, 2 H, ArH), 5.93 (br s, 1 H, NH), 5.02 (t, *J* 8.4 Hz, 1 H, α-H), 3.65 (d, *J* 8.4 Hz, 2 H, β-H), 1.33 (s, 9 H, CMe_3); δ_C 168.3, 167.1, 147.4, 145.4, 135.1, 131.6, 130.3, 124.3, 124.2, 56.4, 52.4, 35.2, 29.1; *m/z* (%) 395 (M^+, 5%), 352 (5), 341 (10), 256 (20), 236 (5), 213 (10); (Found: C, 63.6; H, 5.3; N, 10.5. Calc. for $C_{21}H_{21}N_3O_5$: C, 63.8; H, 5.3; N, 10.6%).

(*R*)-*N*-*tert*-Butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide 78b

This compound was prepared from (*R*)-*N*-phthaloyl-*p*-nitrophenylalanine **110**, as described above for the synthesis of the corresponding racemate, and obtained in 72% yield, m.p. 230 °C (dec.); $[\alpha]_D^{25}$ +117.0° (c, 0.227 in $CHCl_3$).

(*S*)-*N*-*tert*-Butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide

This compound was prepared from (*S*)-*N*-phthaloyl-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 79% yield, m.p. 230 °C (dec.); $[\alpha]_D^{21}$ -120.8° (c, 0.418 in $CHCl_3$).

(2*RS*,3*RS*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide and

(2*RS*,3*SR*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide

To a solution of (*RS*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (771 mg, 1.95 mmol) in a mixture of carbon tetrachloride and dichloromethane (4:1, 50 ml), NBS (695 mg, 3.90 mmol) was added and the mixture was heated at reflux for 3 h, whilst being irradiated with a 300 W sunlamp. The mixture was then allowed to cool to room temperature, then it was filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give a 1:1 mixture of the title compounds as a colourless solid (905 mg, 98%), m.p. 194-210 °C. ν_{max}/cm^{-1} 3380,

3350, 2950, 2920, 2850, 1775, 1715, 1670, 1520, 1460, 1380, 1350, 1280, 1220, 1110, 1090, 1060, 880, 720, 700; *m/z* (FAB) (%) 476 (MH^+, 40%), 474 (MH^+, 40%), 420 (20), 418 (20), 295 (30), 154 (100), 136 (90); (Found: C, 53.1; H, 4.2; N, 8.9. Calc. for $C_{21}H_{20}BrN_3O_5$: C, 53.2; H, 4.3; N, 8.9%). Fractional recrystallisation of the mixture of isomers from a combination of dichloromethane and light petroleum afforded a sample of (2*RS*,3*SR*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide; δ_H 8.08 (d, *J* 8.9 Hz, 2 H, ArH), 7.79-7.64 (m, 4 H, Phth), 7.56 (d, *J* 8.9 Hz, 2 H, ArH), 6.23 (br s, 1 H, NH), 6.18 (d, *J* 11.4 Hz, 1 H, β-H), 5.29 (d, *J* 11.4 Hz, 1 H, α-H), 1.41 (s, 9 H, CMe_3); δ_C 167.5, 164.8, 145.3, 135.1, 131.2, 129.4, 129.3, 124.5, 124.3, 60.7, 52.9, 46.4, 29.1. The structure of this material was confirmed through X-ray crystallographic analysis (Appendix 6). The ^1H and ^{13}C NMR spectra of the mixture of diastereomers showed resonances for the (2*RS*,3*RS*)-isomer, δ_H 8.26 (d, *J* 8.9 Hz, 2 H, ArH), 7.98-7.81 (m, 4 H, Phth), 7.77 (d, *J* 8.9 Hz, 2 H, ArH), 6.27 (br s, 1 H, NH), 6.20 (d, *J* 11.7 Hz, 1 H, β-H), 5.09 (d, *J* 11.7 Hz, 1 H, α-H), 1.11 (s, 9 H, CMe_3); δ_C 168.3, 163.9, 148.3, 135.3, 131.6, 130.1, 130.0, 124.6, 124.5, 62.7, 52.4, 49.1, 28.8.

(2*S*,3*S*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide 72a and (2*S*,3*R*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide 71b

A 1:1 mixture of these compounds was prepared from (*R*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide **78b**, as described above for the synthesis of the corresponding racemate, and obtained in 95% yield.

(2*R*,3*R*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide and

(2*R*,3*S*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide

A 1:1 mixture of the title compounds was prepared in quantitative yield from (*S*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate.

Treatment of (*R*)-3-Bromo-*N*-phthaloylvaline Methyl Ester 33 with Silver Nitrate in Aqueous Acetone.

To a solution of the bromide **33** (0.66 g, 1.9 mmol) in acetone (10 ml), a solution of silver nitrate (0.49 g, 2.9 mmol) in water (10 ml) was added. The resultant mixture was stirred at room temperature in the dark for 14 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane and the organic extracts were dried and concentrated under reduced pressure to afford an oil which was chromatographed. Elution gave the α,β-dehydrovaline derivative **98** (40 mg, 8%), m.p. 81-82 °C. δ_H 8.10-7.40 (m, 4 H, Phth), 3.68 (s, 3 H, OMe), 2.43 (s, 3 H, Me), 1.88 (s, 3 H, Me'); (Found: C, 64.7; H, 5.1; N, 5.4. Calc. for $C_{14}H_{13}NO_4$: C, 64.8; H, 5.1; N, 5.4%). Continued elution afforded the β,γ-dehydrovaline derivative **38** (0.15 g, 34%); ν_{max}/cm^{-1} 2950, 1780, 1748, 1728, 1470, 1440, 1386, 1293, 1245, 1203, 1113, 915, 717; δ_H 7.92-7.75 (m, 4 H, Phth), 5.38 (br s, 1 H, γ-H), 5.14 (br s, 1 H, γ-H'), 5.11 (s, 1 H, α-H), 3.79 (s, 3 H, OMe), 1.92 (s, 3 H, β-Me); *m/z* (%) 259 (M^+, 8%), 227 (20), 200 (100). Further elution gave the β-hydroxyvaline derivative **34** (0.21 g, 43%), m.p. 86-87 °C; ν_{max}/cm^{-1} 3544, 1767, 1725, 1275, 717; δ_H 7.91-7.80 (m, 4 H, Phth), 4.91 (s, 1 H, α-H), 4.41 (br s, 1 H, OH), 3.77 (s, 3 H, OMe), 1.53 (s, 3 H, Me), 1.31 (s, 3 H, Me');

m/z (%) 262 (M-CH_3^+, 10%), 246 (5), 230 (28), 219 (100), 188 (74), 187 (98), 160 (74); (Found: C, 60.6; H, 5.5; N, 5.1. Calc. for $C_{14}H_{15}NO_5$: C, 60.6; H, 5.5; N, 5.1%). Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed the alcohol **34** and the alkenes **98** and **38** to be present in the ratio *ca.* 3.5 : 1 : 3.5.

Treatment of (*R*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylvalinamide 73 with Silver Nitrate in Aqueous Acetone.

The reaction of the bromide **73**, carried out as described above for the reaction of the ester **33**, afforded an oil which was chromatographed. Elution gave the β,γ-dehydrovaline derivative **112** as a colourless oil (26%); ν_{max}/cm^{-1} 3450, 2975, 2950, 1780, 1710, 1695, 1525, 1460, 1475, 1385; δ_H 7.89-7.73 (m, 4 H, Phth), 6.28 (br s, 1 H, NH), 5.27 (s, 1 H), 5.23 (s, 1H), 5.21 (s, 1H), 1.89 (s, 3 H, Me), 1.43 (s, 9 H, CMe_3); δ_C 169.8, 167.3, 141.6, 136.1, 133.8, 125.4, 119.5, 62.5, 53.7, 30.5, 22.8; *m/z* (%) 300 (M^+, 5%), 200 (100); (Found: C, 68.0; H, 7.0; N, 9.0. Calc. for $C_{17}H_{20}N_2O_3$: C, 68.0; H, 6.7; N, 9.3%). Further elution afforded the alcohol **111**, as colourless crystals after recrystallisation from a mixture of ether and light petroleum (63%), m.p. 135-136 °C; ν_{max}/cm^{-1} 3328, 3084, 2972, 2928, 2248, 1774, 1720, 1660, 1614, 1550, 1470, 1384, 1224, 1176, 1144, 1088, 1048, 992, 956, 912, 878, 788, 774, 724, 646; δ_H 7.84-7.79 (m, 2 H, Phth), 7.73-7.69 (m, 2 H, Phth), 7.30 (br s, 1 H, NH), 4.61 (s, 1 H, α-H), 4.25 (br s, 1 H, OH), 1.41 (s, 3 H, Me), 1.30 (s, 9 H, CMe_3), 1.22 (s, 3 H, Me); *m/z* (%) 318 (M^+, 50), 300 (10), 259 (50), 201 (100), 187 (100), 160 (95); (Found: C, 64.3; H, 7.2; N, 8.7. Calc. for $C_{17}H_{22}N_2O_4$: C, 64.1; H, 7.0; N, 8.8%). The structure of the alcohol **111** was confirmed through X-ray crystallographic analysis (Appendix 3).[218] Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed the alcohol **111** and the alkene **112** were present in the ratio *ca.* 2 : 1.

Treatment of (2*S*,3*S*)-3-Bromo-*N*-phthaloyl-*p*-nitrophenylalanine Methyl Ester 71a with Silver Nitrate in Aqueous Acetone.

To a solution of the bromide **71a** (50 mg, 0.12 mmol) in acetone (3 ml), a solution of silver nitrate (25 mg, 0.15 mmol) in water (2 ml) was added. The resultant mixture was stirred at 65 °C in the dark for 48 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane and the organic extracts were dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the (*Z*)-*p*-nitrophenylalanine derivative **115** as large colourless prisms (34 mg, 84%), m.p. 133-134 °C; ν_{max}/cm^{-1} 1780, 1720, 1600, 1530, 1345; δ_H 8.16 (d, *J* 8.8 Hz, 2 H, ArH), 8.13 (s, 1 H, β-H), 7.92-7.83 (m, 4 H, Phth), 7.55 (d, *J* 8.8 Hz, 2 H, ArH), 3.87 (s, 3 H, OMe); *m/z* (%) 352 (M^+, 90%), 342 (63), 293 (41), 292 (46), 247 (24), 218 (15), 190 (18), 166 (21), 104 (100), 76 (73); *m/z* 352.068 (M^+) [Calc. for $C_{18}H_{12}N_2O_6$ (M^+) *m/z* 352.070]. Neither the alcohol **114** nor the alkene **116** were detected in the crude product.

Treatment of (2*S*,3*R*)-3-Bromo-*N*-phthaloyl-*p*-nitrophenylalanine Methyl Ester 71b with Silver Nitrate in Aqueous Acetone.

The reaction of the bromide **71b**, carried out as described above for the reaction of the stereoisomer **71a**, afforded an oil which was chromatographed. Elution afforded a 2:3 mixture of the dehydrophenylalanine derivatives **115** and **116** as a viscous oil (25%). The ^1H NMR spectrum of the mixture showed resonances for the (*Z*)-isomer **115**, identical to those described above, and signals for the (*E*)-isomer **116**, δ_H 8.26 (d, *J* 8.7 Hz, 2 H, ArH), 7.98-7.80 (m, 4 H, Phth), 7.60 (d, *J* 8.7 Hz, 2 H, ArH), 7.28 (s, 1 H, β-H), 3.72 (s, 3 H, OMe). Continued elution gave the β-hydroxy-*p*-nitrophenylalanine derivative **114** as colourless needles (63%), after recrystallisation

from a mixture of dichloromethane and light petroleum, m.p. 183-185 °C. ν_{max}/cm^{-1} 3604, 3421, 1779, 1752, 1714, 1614, 1526, 1392, 1352, 1182; δ_H 8.13 (d, *J* 8.9 Hz, 2 H, ArH), 7.82-7.73 (m, 4 H, Phth), 7.54 (d, *J* 8.9 Hz, 2 H, ArH), 5.79 (dd, *J* 4.4, 10.0 Hz, 1 H, β-H), 5.53 (d, *J* 4.4 Hz, 1 H, α-H), 5.34 (d, *J* 10.0 Hz, 1 H, OH), 3.89 (s, 3 H, OMe); *m/z* (FAB) (%) 371 ($M+H^+$, 9%), 353 (3), 321 (3), 307 (11), 289 (9), 219 (3), 154 (100), 137 (66), 136 (79), 107 (28), 89 (33), 77 (31).

(2*RS*,3*SR*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide

To a solution of a 1:1 mixture of (2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (265 mg, 0.56 mmol) in acetone (10 ml) and water (10 ml), silver sulfate (263 mg, 0.84 mmol) was added and the suspension was heated at 65 °C in the dark for 3 days. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with saturated brine, then dried and concentrated under reduced pressure. The residue was chromatographed, to give the title compound as an off-white crystalline solid (154 mg, 67%), m.p. 209-210 °C. ν_{max}/cm^{-1} 3700, 3400, 3160, 3000, 2920, 2270, 1830, 1800, 1720, 1650, 1610, 1570, 1480, 1390, 1110; δ_H 8.14 (d, *J* 8.8 Hz, 2 H, ArH), 7.81-7.71 (m, 4 H, Phth), 7.54 (d, *J* 8.8 Hz, 2 H, ArH), 6.01 (br s, 1 H, NH), 5.68 (dd, *J* 4.9, 8.3 Hz, 1 H, β-H), 5.17 (d, *J* 4.9 Hz, 1 H, α-H), 4.93 (d, *J* 8.3 Hz, 1 H, OH), 1.37 (s, 9 H, CMe_3); δ_C 168.6, 164.9, 147.4, 134.7, 131.1, 126.6, 123.9, 123.6, 71.7, 59.9, 52.3, 28.6; *m/z* (%) 412 ($M+H^+$, 1%), 384 (2), 378 (2), 356 (1), 294 (82), 260 (100), 204 (30); (Found: C, 61.0; H, 5.3; N, 10.0. Calc. for $C_{21}H_{21}N_3O_6$: C, 61.3; H, 5.2; N, 10.2%).

(2*R*,3*S*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide 117

The title compound **117** was prepared from a 1:1 mixture of the bromides **72a** and **72b**, as described above for the synthesis of the corresponding racemate, and obtained in 64% yield, m.p. 226-228 °C; $[\alpha]_D^{25}$ +84.1° (c, 0.453 in $CHCl_3$). There was no indication of the presence of either of the alkenes **120** or **121** in the ^1H NMR spectrum of the crude reaction mixture.

(2*S*,3*R*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide 132

The title compound **132** was prepared from a 1:1 mixture of (2*R*,3*R*)- and (2*R*,3*S*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 62% yield, m.p. 220-222 °C; $[\alpha]_D^{20}$ -83.1 (c, 0.083 in $CHCl_3$).

Treatment of (2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-Bromo-*N*-phthaloyl-*p*-nitrophenylalanine Methyl Ester with Silver Sulfate in Aqueous Acetone.

A 1:1 mixture of (2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-bromo-*N*-phthaloyl-*p*-nitrophenylalanine methyl ester was treated with silver sulfate in aqueous acetone, as described for the reaction of the bromoamides **72a** and **72b**. Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed that the racemate of the alcohol **114** and the alkenes **115** and **116** were present in the ratio *ca.* 1:1:20.

Treatment of (2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide with Silver Nitrate in Aqueous Acetone.

The reaction of a 1:1 mixture of (2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, carried out as described above for the reaction of the bromoester **71a**, afforded an oil which was chromatographed. Elution afforded the nitrate **118** (19%), m.p. 192 °C (dec.). ν_{max}/cm^{-1} 3720, 3460, 3390, 3190, 3020, 2950, 2290, 1830, 1800, 1740, 1670, 1630, 1550, 1490, 1400, 1370, 1320, 1300, 1240, 1190, 1110; δ_H 8.30 (d, *J* 8.9 Hz, 2 H, ArH), 7.92-7.81 (m, 4 H, Phth), 7.77 (d, *J* 8.9 Hz, 2 H, ArH), 7.19 (d, *J* 10.7 Hz, 1 H, β-H), 5.89 (br s, 1 H, NH), 4.90 (d, *J* 10.7 Hz, 1 H, α-H), 1.14 (s, 9 H, CMe_3); δ_C 167.6, 163.1, 148.6, 141.8, 134.9, 131.2, 129.1, 124.1, 124.1, 78.1, 57.8, 52.2, 28.3; *m/z* (%) 457 ($M+H^+$, 30%), 393 (15), 307 (40), 286 (100), 260 (30). Continued elution gave (2*RS*,3*SR*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (54%), identical to the sample obtained as described above. There was no indication of the presence of either of the alkenes **115** or **116** in the ^1H NMR spectrum of the crude product.

(2*RS*,3*SR*)-3-Hydroxy-*p*-nitrophenylalanine

A suspension of (2*RS*,3*SR*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (85 mg, 0.21 mmol) in a 2:1 mixture of 6N hydrochloric acid and acetic acid (10 ml) was heated at reflux for 5 h and stirred for 16 h at room temperature, before concentration under reduced pressure. Water (10 ml) was added to the residue, then the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (10 ml) and to that solution aniline (0.7 ml) in dichloromethane (10 ml) was added. The mixture was allowed to stand at 4 °C for 24 h

and the material which crystallised was separated by filtration and washed with dichloromethane, to give the title compound as an off-white solid (27 mg, 58%), m.p. 192-193 °C (Lit.[219] 187-188 °C (dec.)). ν_{max}/cm^{-1} 3550, 3200, 2920, 2870, 1610, 1590, 1530, 1460, 1380, 1350, 1200, 1110, 1010, 865, 855, 740, 710; δ_H (CF_3CO_2D) 8.33 (d, *J* 8.8 Hz, 2 H, ArH), 7.74 (d, *J* 8.8 Hz, 2 H, ArH), 5.77 (d, *J* 3.9 Hz, 1 H, β-H), 4.70 (d, *J* 3.9 Hz, 1 H, α-H); δ_C (D_2O) 173.5, 149.6, 149.0, 129.1, 126.0, 72.7, 62.5; *m/z* (FAB) (%) 227 ($M+H^+$, 46%). The ^1H NMR spectral data for this compound is consistent with that reported.[189]

(2*R*,3*S*)-3-Hydroxy-*p*-nitrophenylalanine 133

This compound was prepared from the alcohol **117**, as described above for the synthesis of the corresponding racemate, and obtained in 69% yield, m.p. 200-203 °C (Lit.[189] 174-176 °C); $[\alpha]_D^{25}$ +35.3° (c, 0.102 in 1N HCl) (Lit.[189] $[\alpha]_D^{25}$ +27° (c, 0.5 in H_2O)).

(2*S*,3*R*)-3-Hydroxy-*p*-nitrophenylalanine 74

This compound was prepared from the (2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide **132**, as described above for the synthesis of the corresponding racemate, and obtained in 54% yield, m.p. 204-205 °C; $[\alpha]_D^{20}$ -36.4° (c, 0.176 in 1N HCl) (Lit.[124] $[\alpha]_D^{21.5}$ -33.8° (c, 5 in 1N HCl)).

Competitive Hydrolysis Reactions of the Bromides 18a, 18b, 20a and 20b using Silver Nitrate in Aqueous Acetone.

The relative rates of reaction of the bromides **18a**, **18b**, **20a** and **20b** with silver nitrate were determined by treating 1-3 molar equivalents of the substrates at a concentration of approximately 1.0 mM in aqueous acetone (1:1, v/v) with the silver salt

(1.4 equiv.) at room temperature for 16 h, in the presence of *N-tert*-butylbenzamide (0.1-0.5 equiv.) as an internal standard. The reaction mixtures were worked up as described for the preparative studies, then analysed by ^{1}H NMR spectroscopy. Integration of peaks characteristic of the residual bromides **18a**, **18b**, **20a** and **20b** and the internal standard, and comparison with the spectra of the corresponding starting mixtures, were used to determine the percentage of each substrate remaining, from which the ratios of the logarithms of those percentages were used to calculate the relative rates of reaction. The data obtained from these experiments are summarised in Appendix 7.

Competitive Hydrolysis Reactions of the Bromides 33 and 73 using Silver Nitrate in Aqueous Acetone.

The relative rates of reaction of the bromides **33** and **73** with silver nitrate were determined in an identical manner to that described above for the competitive reactions of the bromophenylalanine derivatives **18a**, **18b**, **20a** and **20b**. The data obtained from these experiments are summarised in Appendix 8.

Competitive Hydrolysis Reactions of the Bromides 71a, 71b, 72a and 72b using Silver Sulfate in Aqueous Acetone.

The relative rates of reaction of the bromides **71a**, **71b**, **72a** and **72b** with silver sulfate were determined in an identical manner to that described above for the competitive reactions of the bromophenylalanine derivatives **18a**, **18b**, **20a** and **20b**, except that silver sulfate was used in place of silver nitrate and the mixtures were heated at 65 °C for 48 h. The data obtained from these experiments are summarised in Appendix 9.

Competitive Hydrolysis Reactions of the Bromides 20a and 20b using Silver Nitrate in Deuterium Oxide and Acetone.

The relative rates of reaction of the bromides **20a** and **20b** with silver nitrate were determined in an identical manner to that described above for the competitive reactions of the bromophenylalanine derivatives **18a**, **18b**, **20a** and **20b**, except that deuterium oxide was used in place of water. The data obtained from these experiments are summarised in Appendix 10.

(*S*)-*O*-Acetyl-*N*-*tert*-butyl-N^{α}-phthaloyltyrosinamide 79b

The title compound **79b** was prepared from (*S*)-*O*-acetyl-N^{α}-phthaloyltyrosine **136**[59] (537 mg, 1.5 mmol), using the procedure described above for the preparation of the phenylalaninamide **19** (537 mg, 1.5 mmol), by treatment with triethylamine, ethyl chloroformate and then *tert*-butylamine, and isolated as a white solid (468 mg, 75%). δ_H 7.81-7.76 (m, 4 H, Phth), 7.20 (d, *J* 8.4 Hz, 2 H, ArH), 6.93 (d, *J* 8.4 Hz, 2 H, ArH), 5.81 (br s, 1 H, NH) 4.97 (dd, *J* 6.9, 10.1 Hz, 1 H, α-H), 3.57 (dd, *J* 6.9, 14.2 Hz, 1 H, β-H), 3.48 (dd, *J* 10.1, 14.2 Hz, 1 H, β'-H), 2.23 (s, 3 H, OAc), 1.31 (s, 9 H, CMe_3). The ^{1}H NMR spectral data for this material are consistent with reported values.[59]

(2*R*,3*R*)-*O*-Acetyl-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyltyrosinamide 81b and (2*R*,3*S*)-*O*-Acetyl-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyltyrosinamide 81a

The title compounds **81a** and **81b** were prepared from (*S*)-*N*-*tert*-butyl-*O*-acetyl-N^{α}-phthaloyltyrosinamide **79b** (205 mg, 0.50 mmol)[59] as described above for the preparation of the bromophenylalanine derivatives **18a** and **18b**, by treatment with NBS (107 mg, 0.60 mmol) in carbon tetrachloride at reflux whilst irradiating with a 300 W sunlamp (241 mg, 99%). **81b** δ_H 7.96-7.77 (m, 4 H, Phth), 7.63 (d, *J* 8.6 Hz, 2 H, ArH), 7.15 (d, *J* 8.6 Hz, 2 H, ArH), 6.20 (d, *J* 11.8 Hz, 1 H, β-H), 5.78 (br s, 1 H, NH) 5.15 (d, *J* 11.8 Hz, 1 H, α-H), 2.32 (s, 3 H, OAc), 1.06 (s, 9 H, CMe_3); **81a** δ_H 7.76-7.61 (m, 4 H, Phth), 7.39 (d, *J* 8.7 Hz, 2 H, ArH), 6.95 (d, *J* 8.7 Hz, 2 H, ArH), 6.36 (br s, 1 H, NH), 6.08 (d, *J* 11.5 Hz, 1 H, β-H), 5.29 (d, *J* 11.5 Hz, 1 H, α-H), 2.21 (s, 3 H, OAc), 1.40 (s, 9 H, CMe_3). The ^{1}H NMR spectral data for this material are consistent with literature values.[96]

(2*R*,3*R*)-*O*-Acetyl-3-bromo-*N*-phthaloyltyrosine Methyl Ester 80b and (2*R*,3*S*)-*O*-Acetyl-3-bromo-*N*-phthaloyltyrosine Methyl Ester 80a

The title compounds **80a** and **80b** were prepared from (*S*)-*O*-acetyl-N^{α}-phthaloyltyrosine methyl ester **79a** (695 mg, 1.97 mmol)[59] by treatment with NBS (420 mg, 2.36 mmol) using the procedure described above for the preparation of the bromophenylalanine derivatives **18a** and **18b** (799 mg, 94%). **80b** δ_H 7.98-7.91 (m, 2 H, Phth), 7.85-7.77 (m, 2 H, Phth), 7.61 (d, *J* 8.8 Hz, 2 H, ArH), 7.14 (d, *J* 8.8 Hz, 2 H, ArH), 6.03 (d, *J* 11.2 Hz, 1 H, β-H), 5.45 (d, *J* 11.2 Hz, 1 H, α-H), 3.57 (s, 3 H, OMe), 2.32 (s, 3 H, OAc); **80a** δ_H 7.74-7.61 (m, 4 H, Phth), 7.37 (d, *J* 8.7 Hz, 2 H, ArH), 6.93 (d, *J* 8.7 Hz, 2 H, ArH), 5.93 (d, *J* 10.5 Hz, 1 H, β-H), 5.57

(d, *J* 10.5 Hz, 1 H, α-H), 3.82 (s, 3 H, OMe), 2.20 (s, 3 H, OAc). The ^{1}H NMR spectral data for this material are consistent with literature values.[96]

Competitive Reactions of the Phenylalanine, Nitrophenylalanine and Tyrosine Derivatives 17, 19, 78a, 78b, 79a and 79b with NBS

The relative rates of reaction of the derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b** were determined by treating various mixtures of the substrates in carbon tetrachloride with NBS (*ca.* 1.0 equiv.) at reflux under nitrogen and in the presence of *tert*-butylbenzamide (0.1-0.5 equiv.) as an internal standard, whilst being irradiated with a 300 W sunlamp. After being allowed to cool to room temperature, the mixtures were filtered and concentrated under reduced pressure and then analysed using ^{1}H NMR spectroscopy. The data obtained from these experiments are summarised in Appendix 11.

Competitive Reactions of the Bromides 18a, 18b, 20a, 20b, 71a, 71b, 72a, 72b, 80a, 80b, 81a and 81b with Triphenyltin Hydride

The relative rates of reaction of the bromides **18a**, **18b**, **20a**, **20b**, **71a**, **71b**, **72a**, **72b**, **80a**, **80b**, **81a** and **81b** were determined by treating various mixtures of the substrates in benzene with triphenyltin hydride (*ca.* 1.0 equiv.) at reflux under nitrogen and in the presence of *tert*-butylbenzamide (0.1-0.5 equiv.) as an internal standard, whilst being irradiated with a 300 W sunlamp. After being allowed to cool to room temperature, the mixtures were concentrated under reduced pressure and then analysed using ^{1}H NMR spectroscopy. The data obtained from these experiments are summarised in Appendix 12.

Treatment of (2*S*,3*R*)-3-Deutero-*N*-phthaloylphenylalanine Methyl Ester 26 with NBS

To a solution of (2*S*,3*R*)-3-deutero-*N*-phthaloylphenylalanine methyl ester **26**[58] (5.8 mg, 16 μmol) in carbon tetrachloride (2 ml) was added NBS (3.2 mg, 18 μmol). The resultant mixture was heated at reflux for 2 h whilst being irradiated with a 300 W sunlamp, then was allowed to cool to room temperature and was filtered. Following concentration of the solution under reduced pressure, the crude product was analysed using ^{1}H NMR spectroscopy, which showed the diastereomeric bromides **137a** and **137b** in the ratio *ca.* 1:1. The percentage deuterium content of the bromides **137a** and **137b** was determined from the ^{1}H NMR spectrum and from the mass spectrum of the crude product as described in Chapter 3 of the Results and Discussion of this thesis, and the results of this experiment are summarised in Table 3.4.

Treatment of (2*S*,3*S*)-3-Deutero-*N*-phthaloylphenylalanine Methyl Ester 29 with NBS

The reaction of (2*S*,3*S*)-3-deutero-*N*-phthaloylphenylalanine methyl ester **29**[58] with NBS was carried out in an identical manner to that described above for the reaction of the deuteride **26** with NBS, and the crude product was analysed using ^{1}H NMR spectroscopy and mass spectrometry. The bromides **137a** and **137b** were present in the crude product in the ratio *ca.* 1:1. The percentage deuterium content of the bromides **137a** and **137b** determined from the ^{1}H NMR and mass spectra of the crude product is given in Chapter 3 of the Results and Discussion of this thesis, and the results obtained from this experiment and those of a duplicate experiment are summarised in Table 3.4.

Treatment of (2*S*,3*R*)-3-Deutero-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide 31b with NBS

The reaction of (2*S*,3*R*)-3-deutero-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **31b**[59] with NBS was carried out in an identical manner to that described above for the reaction of the deuteride **26** with NBS, and the crude product was analysed using ^{1}H NMR spectroscopy and mass spectrometry. The bromides **138a** and **138b** were present in the crude product in the ratio *ca.* 1:1. The percentage deuterium content of the bromides **138a** and **138b**, determined from the ^{1}H NMR and mass spectra of the crude product, is given in Chapter 3 of the Results and Discussion of this thesis and the results of this experiment and those of a duplicate experiment are summarised in Table 3.4.

Treatment of (2*S*,3*S*)-3-Deutero-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide 31a with NBS

The reaction of (2*S*,3*S*)-3-deutero-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide **31a**[59] with NBS was carried out in an identical manner to that described above for the reaction of the deuteride **26** with NBS, and the crude product was analysed using ^{1}H NMR spectroscopy and mass spectrometry. The bromides **138a** and **138b** were present in the crude product in the ratio *ca.* 1:1. The percentage deuterium content of the bromides **138a** and **138b** was determined from the ^{1}H NMR and mass spectra of the crude product as described in Chapter 3 of the Results and Discussion of this thesis, and the results of this experiment and those of a duplicate experiment are summarised in Table 3.4.

Treatment of the Phenylalaninamide 19 with Bromine and Aqueous Potassium Hydroxide

N-tert-Butyl-N^{α}-phthaloylphenylalaninamide **19** (507 mg, 1.5 mmol) was dissolved in bromine (75 μl, 1.5 mmol), then the resultant solution was cooled to 0 °C in an ice bath. Aqueous potassium hydroxide solution (*ca.* 1 ml, 50%) was added to the solution until the bromine colour was dissipated, then the mixture was stirred for 3 h and sodium chloride (350 mg, 6.0 mmol) was added. The mixture was extracted with chloroform (4 x 3 ml), then the organic extracts were combined and dried, and the solution was concentrated under reduced pressure, affording a crude product (395 mg, 63%). Analysis of the crude product using ^{1}H NMR spectroscopy showed *p*-bromo-*N-tert*-butyl-N^{α}-phthaloylphenylalaninamide **139** comprised *ca.* 80% of that mixture. δ_H 7.82-7.70 (m, 4 H, Phth), 7.31 (br d, *J* 8.4 Hz, 2 H, ArH), 7.05 (br d, *J* 8.4 Hz, 2 H, ArH), 5.87 (br s, 1 H, NH), 4.96 (t, *J* 8.5 Hz, 1 H, α-H), 3.49 (d, *J* 8.5 Hz, 2 H, β-H), 1.33 (s, 9 H, CMe_3); *m/z* (%) 430 ($M^{+\bullet}$, 58%), 428 ($M^{+\bullet}$, 58), 349 (55), 329 (100), 312 (12), 310 (12), 283 (25), 281 (24), 249 (94), 173 (85), 104 (67), 76 (60). Purification of this material using chromatography on silica was unsuccessful due to decomposition. Hence, *p*-bromo-*N-tert*-butyl-N^{α}-phthaloylphenylalaninamide **139** was not further purified or characterised.

N-Bromo-N-tert-butyl-N^{α}-phthaloylphenylalaninamide 92

tert-Butylhypobromite in carbon tetrachloride (1 ml, 0.4 M)[196] was added to the phenylalanine derivative **19** (5 mg, 14 μmol) and the resultant solution was stirred at room temperature for 16 h in the dark. The solution was concentrated under reduced pressure, and the crude product was analysed using ^{1}H NMR spectroscopy, which showed that the title compound **92** comprised *ca.* 90% of that mixture. ν_{max}(neat)/cm^{-1} 3060, 2970, 2920, 2850, 1775, 1715, 1520, 1470, 1450, 1375, 1220, 1100, 910, 880,

740, 720, 700; δ_H 7.79-7.67 (m, 4 H, ArH), 7.18 (m, 5 H, Ph), 5.69 (dd, *J* 5.4, 10.5 Hz, 1 H, α-H), 3.59 (dd, *J* 10.5, 14.4 Hz, 1 H, β-H), 3.52 (dd, *J* 5.4, 14.4 Hz, 1 H, β-H'), 1.48 (s, 9 H, CMe_3). The crude material was not purified and was therefore used in subsequent reactions without further characterisation.

Photolysis of *N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide 92.

A solution of the *N*-bromoamide **92** (6 mg, 14 μmol) in carbon tetrachloride (1 ml) at reflux under nitrogen was photolysed for 5 mins with a 300 W sunlamp, then the solution was concentrated under reduced pressure. Analysis of the crude product using ^{1}H NMR spectroscopy showed that a 1:1 mixture of the β-bromides **20a** and **20b** and the amide **19** were present in the ratio *ca.* 2:1.

(2*S*,3*S*)-3-Deutero-*N*-bromo-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide 140a

The title compound **140a** was prepared in approximately 95% yield and with *ca.* 98% deuterium content from the (2*S*,3*S*)-amide **31a**[58,59] as determined by analysis of the crude product using ^{1}H NMR spectroscopy, by treatment with *tert*-butyl hypobromite, using the procedure described above for the preparation of the *N*-bromophenylalanine derivative **92**. δ_H 7.78 (m, 2 H, ArH), 7.68 (m, 2 H, ArH), 7.17 (m, 5 H, Ph), 5.66 (d, *J* 11.4 Hz, 1 H, α-H), 3.56 (br d, *J* 11.4 Hz, 1 H, β-H), 1.47 (s, 9 H, CMe_3). The crude material was not purified and was therefore used in the subsequent reaction without further characterisation. The (2*S*,3*R*)-diastereomer **140b** was not detected in the crude product.

(2*S*,3*R*)-3-Deutero-*N*-bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide 140b

The title compound **140b** was prepared in approximately 60% yield and with *ca.* 98% deuterium content from the (2*S*,3*R*)-amide **31b**[58,59] as determined using ^{1}H NMR spectroscopy, by treatment with *tert*-butyl hypobromite, using the procedure described above for the preparation of the *N*-bromophenylalanine derivative **92**. δ_H 7.79 (m, 2 H, ArH), 7.68 (m, 2 H, ArH), 7.19 (m, 5 H, Ph), 5.66 (d, *J* 4.5 Hz, 1 H, α-H), 3.51 (br d, *J* 4.5 Hz, 1 H, β-H), 1.47 (s, 9 H, CMe_3). The crude material was not purified and was therefore used without further characterisation. The (2*S*,3*S*)-diastereomer **140a** was not detected in the ^{1}H NMR spectrum of the crude product.

Photolysis of (2*S*,3*S*)-3-Deutero-*N*-bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-phenylalaninamide 140a

A solution of the crude *N*-bromoamide **140a** at a concentration of approximately 1.5 mM in carbon tetrachloride (1 ml) at reflux under an atmosphere of nitrogen was irradiated for 5 mins with a 300 W sunlamp. The solution was concentrated under reduced pressure, then the crude product was analysed using ^{1}H NMR spectroscopy which showed a 1:1 mixture of the β-bromides **138a** and **138b** and the amide **31a** were present in the ratio *ca.* 2:1. The percentage deuterium content of the bromides **138a** and **138b** determined from the ^{1}H NMR and mass spectra as described in Chapter 3 of the Results and Discussion of this thesis for the reactions of the deuterides **26**, **29**, **31a** and **31b** with NBS is summarised in Table 4.1.

Photolysis of (2*S*,3*R*)-3-Deutero-*N*-bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-phenylalaninamide 140b

A solution of the crude *N*-bromoamide **140b** at a concentration of approximately 2.3 mM in carbon tetrachloride (1 ml) at reflux under an atmosphere of nitrogen was irradiated for 5 mins with a 300 W sunlamp. The solution was concentrated under reduced pressure, then the crude product was analysed using ^{1}H NMR spectroscopy which showed a 1:1 mixture of the β-bromides **138a** and **138b** and the amide **31b** were present in the ratio *ca.* 1:1. The percentage deuterium content of each of the bromides **138a** and **138b** determined from the ^{1}H NMR and mass spectra as described in Chapter 3 of the Results and Discussion of this thesis for the reactions of the deuterides **26**, **29**, **31a** and **31b** with NBS is summarised in Table 4.1.

Competitive Reaction of the Phenylalaninamide 19 and *tert*-Butyltoluene with NBS.

The relative rate of reaction of *N*-phthaloylphenylalaninamide **19** (10.0 mg, 29 μmol) and *p*-*tert*-butyltoluene (5.1 μl, 28 μmol) with NBS was determined by treating an approximately equimolar ratio of each substrate in carbon tetrachloride (3 ml) with NBS (3.7 mg, 21 μmol) at reflux under an atmosphere of nitrogen, whilst irradiating the mixture for 30 mins with a 300 W sunlamp. The mixture was allowed to cool to room temperature, then was filtered and the solution was concentrated under reduced pressure. Analysis of the crude product using ^{1}H NMR spectroscopy showed a 1:1 mixture of the β-bromides **20a** and **20b**, the amide **19**, *p*-*tert*-butyltoluene and *p*-*tert*-butylbenzyl bromide were present in the ratio *ca.* 1:6:2:4. The results of this experiment are summarised in Table 4.2.

Photolysis Reactions of *N*-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide 92 and *tert*-Butyltoluene at a Series of Concentrations.

A sample of the *N*-bromoamide **92** was prepared using the procedure described above, which contained approximately 20% of the amide. This material was dissolved in 25 ml of dichloromethane, of which portions (1.0, 2.0 and 4.0 ml) were taken and concentrated under reduced pressure. To each of these samples was added a solution of *p*-*tert*-butyltoluene at concentrations of 0.92, 1.84 or 3.46 mM in carbon tetrachloride (5.0 ml), and the resultant solutions were heated at reflux for 5 mins while being irradiated with a 300 W sunlamp. The concentrations of the *N*-bromoamide **92** in these experiments were 0.65, 1.30 and 2.60 mM. Following concentration under reduced pressure, the crude mixtures were analysed using ^{1}H NMR spectroscopy and the ratio of the bromides **20a** and **20b** to *tert*-butylbenzyl bromide was measured from the integrals characteristic of each product. The results of these experiments are given in Table 4.3.

(*R*)-*N*-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide 143

The title compound **143** was prepared in *ca.* 80% yield, as determined using ^{1}H NMR spectroscopy, using the procedure described above for the preparation of the *N*-bromophenylalanine derivative **92**, by treatment of the amide **78b** (2.0 mg, 5.5 μmol) with a solution of *tert*-butyl hypobromite in carbon tetrachloride. δ_H 8.07 (d, *J* 6.6 Hz, 2 H, ArH), 7.82-7.71 (m, 4 H, Phth), 7.40 (d, *J* 6.6 Hz, 2 H, ArH), 5.66 (dd, *J* 6.6, 9.3 Hz, 1 H, α-H), 3.64 (d, *J* 9.3 Hz, 1 H, β-H), 3.62 (d, *J* 6.6 Hz, 1 H, β-H'), 1.47 (s, 9 H, CMe_3). The crude material was not purified and was therefore used in the subsequent photolysis reaction without further characterisation.

Photolysis of (*R*)-*N*-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide 143 in the Presence of *p*-*tert*-Butyltoluene

A solution of the crude *N*-bromoamide **143** at a concentration of approximately 1.5 mM and *p*-*tert*-butyltoluene (1 μl, 5.8 μmol) in carbon tetrachloride (3 ml) at reflux under an atmosphere of nitrogen was photolysed for 5 mins with a 300 W sunlamp. The solution was concentrated under reduced pressure, then was analysed using ^{1}H NMR spectroscopy, which showed the presence of a 1:1 mixture of the β-bromides **72a** and **72b**, the amide **78b** and *p*-*tert*-butylbenzyl bromide in the ratio *ca.* 6.6:3.9:1.

***N*-Benzoyl-*p*-methylphenylalanine Methyl Ester 145**

N-Benzoyl-α-bromoglycine methyl ester **7b** was prepared from *N*-benzoylglycine methyl ester **7a**[213] as described previously,[53] by treatment with NBS in carbon tetrachloride under photolytic conditions. Using the procedure of Castelhano *et al.*,[208] 4-methylbenzylmagnesium bromide, prepared from 4-methylbenzyl bromide (4.15 g, 22.4 mmol), magnesium turnings (0.60 g, 24.7 mmol) and a crystal of iodine in ether (50 ml), was added to the bromoglycine derivative **7b** (2.77 g, 10.2 mmol) in ether at -78 °C *via* a cannula. Saturated ammonium chloride solution was added to the mixture, which was then concentrated under reduced pressure. The residue was taken up in dichloromethane and the resultant solution was washed with water, then dried and concentrated under reduced pressure. The crude material was chromatographed on silica, affording the title compound **145** as a colourless oil (687 mg, 23%). ν_{max}(neat)/cm^{-1} 3320, 3060, 3020, 2950. 2925, 2860, 1740, 1650, 1605, 1580, 1525, 1490, 1440, 1215, 810, 715, 695. δ_H 7.75-7.72 (m, 2 H, Bz), 7.51-7.34 (m, 3 H, Bz), 7.10-7.01 (m, 4 H, ArH), 6.76 (br d, *J* 7.8 Hz, 1 H, NH), 5.06 (m, 1 H, α-H), 3.75 (s, 3 H, OMe), 3.25 (dd, *J* 5.9, 13.9 Hz, 1 H, β-H), 3.17 (dd, *J* 5.7, 13.9 Hz, 1 H, β-H'), 2.30 (s, 3 H, Me); δ_C 171.8, 166.6, 136.3, 133.6, 132.5, 131.4, 129.0, 128.8,

128.2, 126.7, 53.4, 52.0, 37.0, 20.7; *m/z* (%) 297 ($M^{+\bullet}$, 5%), 280 (8), 238 (13), 176 (85), 161 (7), 145 (23), 122 (15), 105 (100), 91 (13), 77 (48). *m/z* 297.1365 ($M^{+\bullet}$) [Calc. for $C_{18}H_{19}NO_3$ ($M^{+\bullet}$) *m/z* 297.1364].

_p_-Methylphenylalanine 146

To *N*-benzoylphenylalanine methyl ester **145** (697 mg, 2.3 mmol) was added a 2:1 mixture of 6 N hydrochloric acid and acetic acid (15 ml), and the mixture was heated at reflux for 3 h. The resultant solution was cooled to room temperature, then concentrated under reduced pressure and the residue was dissolved in ethanol (20 ml). To this solution was added aniline (2 ml) in dichloromethane (5 ml) and the solution set aside for 16 h at *ca.* 4 °C. The title compound **146** was isolated by filtration as an off-white powder (211 mg, 51%), m.p. 235-238 °C. ν_{max}/cm^{-1} 3392, 2920, 2851, 2710, 2542, 1618, 1586, 1502, 1445, 1211, 1346, 1322, 1309, 1290, 856, 805; δ_H (D_2O) 7.21 (m, 4 H, ArH), 3.94 (dd, *J* 4.7, 8.0 Hz, 1 H, α-H), 3.23 (dd, *J* 4.7, 14.6 Hz, 1 H, β-H), 3.05 (dd, *J* 8.0, 14.6 Hz, 1 H, β-H'), 2.31 (s, 3 H, Me); *m/z* (%) 179 (M, 0.4%), 135 (20), 105 (100), 91 (13), 77 (15), *m/z* 179.095 ($M^{+\bullet}$) [Calc. for $C_{10}H_{13}NO_2$ ($M^{+\bullet}$) *m/z* 179.095]; (Found C, 65.76; H, 7.72; N, 7.23. Calc. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82%).

_N_-Phthaloyl-_p_-methylphenylalanine 147

A mixture of *p*-methylphenylalanine **146** (100 mg, 0.56 mmol), phthalic anhydride (87 mg, 0.59 mmol) and triethylamine (14 μl) in toluene (7 ml) was heated at reflux for 4 h, in a flask fitted with a Dean-Stark apparatus. The resultant solution was concentrated under reduced pressure, then the residue was partitioned between dichloromethane and 10% hydrochloric acid. The organic solution was washed with

water, then dried and concentrated, yielding the title compound **147** as a white crystalline solid (167 mg, 97%); m.p. 194-196°C. ν_{max}/cm^{-1} 3500, 2920, 2950, 1775, 1715, 1610, 1515, 1470, 1390, 1115, 1100, 1090, 720; δ_H 7.80-7.67 (m, 4 H, Phth), 7.05 (d, *J* 8.2 Hz, 2 H, ArH), 6.99 (d, *J* 8.2 Hz, 2 H, ArH), 5.20 (t, *J* 8.3 Hz, 1 H, α-H), 3.56 (d, *J* 8.3 Hz, 2 H, β-H), 2.23 (s, 3 H, Me); *m/z* (%) 309 ($M^{+\bullet}$, 20%), 264 (7), 246 (9), 162 (100), 130 (19), 105 (55), 91 (13), 77(23); (Found: C, 69.50; H, 4.64; N, 4.09. Calc. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53%).

N-*tert*-Butyl-N^{α}-phthaloyl-*p*-methylphenylalaninamide 94

To a suspension of *N*-phthaloyl-*p*-methylphenylalanine **147** (100 mg, 0.32 mmol) in carbon tetrachloride (3 ml) was added thionyl chloride (75 µl, 1.0 mmol) and pyridine (10 µl), then the mixture was heated at reflux for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, then carbon tetrachloride (3 ml) and *tert*-butylamine (0.1 ml, 1.0 mmol) were added and the mixture was heated at reflux for a further 1 h. The mixture was cooled to room temperature, then washed with 10% hydrochloric acid and water, then dried and concentrated affording the title compound **94** as a white solid (115 mg, 97%), m.p. 210-211 °C. ν_{max}/cm^{-1} 3300, 2920, 2850, 1775, 1715, 1665, 1560, 1460, 1380, 1365, 1300, 1225, 875, 740, 715; δ_H 7.81-7.68 (m, 4 H, Phth), 7.04 (m, 4 H, ArH), 5.82 (br s, 1 H, NH), 4.97 (dd, *J* 6.9, 9.9 Hz, 1 H, α-H), 3.52 (dd, *J* 6.9, 14.1 Hz, 1 H, β-H), 3.43 (dd, *J* 9.9, 14.1 Hz, 1 H, β-H'), 2.23 (s, 3 H, Me), 1.30 (s, 9 H, CMe_3); δ_C 168.0, 167.3, 136.3, 134.0, 133.7, 131.4, 129.2, 128.6, 123.3, 56.6, 51.5, 34.7, 26.5, 20.8; *m/z* (%) 364 ($M^{+\bullet}$, 80%), 305 (15), 264 (100), 246 (43), 217 (56), 202 (22), 173 (98), 105 (86); (Found: C, 72.20; H, 6.57; N, 7.55. Calc. for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.59).

_N_-Phthaloyl-_p_-methylphenylalanine Methyl Ester 93

To a solution of *N*-phthaloyl-*p*-methylphenylalanine **147** (102 mg, 0.33 mmol) in dry methanol (10 ml) was added a catalytic amount of thionyl chloride. The solution was stirred at room temperature for 72 h under anhydrous conditions, then was concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with aqueous sodium bicarbonate solution and water, then was dried and concentrated under reduced pressure affording the title compound **93** as a white crystalline solid (94 mg, 88%); m.p. 115-118 °C. ν_{max}/cm^{-1} 3020, 2950, 2920, 2850, 1775, 1745, 1715, 1615, 1515, 1470, 1425, 1385, 1245, 1200, 1180, 785, 720; δ_H 7.79-7.65 (m, 4 H, Phth), 7.05 (d, *J* 7.9 Hz, 2 H, ArH), 6.98 (d, *J* 7.9 Hz, 2 H, ArH), 5.14 (dd, *J* 5.9, 10.7 Hz, 1 H, α-H), 3.77 (s, 3 H, OMe), 3.56 (dd, *J* 5.9, 14.1 Hz, 1 H, β-H), 3.50 (dd, *J* 10.7, 14.1 Hz, 1 H, β-H'), 2.21 (s, 3 H, Me); δ_C 169.2, 167.3, 136.1, 133.9, 133.4, 131.4, 129.0, 128.5, 123.3, 53.2, 52.7, 34.0, 20.8; *m/z* (%) 323 (M, 9%), 264 (12), 246 (8), 176 (100), 145 (37), 130 (17), 105 (52), 91 (14); *m/z* 323.116 ($M^{+\bullet}$) [Calc. for $C_{19}H_{17}NO_4$ ($M^{+\bullet}$) *m/z* 323.116].

Treatment of _N_-Phthaloyl-_p_-methylphenylalanine Methyl Ester 93 with NBS.

N-Phthaloyl-*p*-methylphenylalanine methyl ester **93** (3.2 mg, 9.9 μmol) was dissolved in carbon tetrachloride (3 ml), then NBS (1.2 mg, 6.7 μmol) was added and the mixture was heated at reflux for 1 h under an atmosphere of nitrogen whilst being irradiated with a 300 W sunlamp. The resultant solution was allowed to cool to room temperature, then was washed with water, then dried and concentrated under reduced pressure. The crude material was analysed using ^{1}H NMR spectrometry, which showed the *p*-bromomethyl compound **149**, the β-bromides **148a** and **148b**, and the ester **93** present in the *ca.* 7.3 : 1 : 9.4 ratio. **149** δ_H 7.82-7.77 (m, 2 H, Phth), 7.73-7.68

(m, 2 H, Phth), 7.22 (d, *J* 8.1 Hz, 2 H, ArH), 7.15 (d, *J* 8.1 Hz, 2 H, ArH), 5.13 (dd, *J* 5.7, 10.8 Hz, 1 H, α-H), 4.39 (s, 2 H, CH_2Br), 3.78 (s, 3 H, OMe), 3.57 (m, 2 H, β-H); **148a** δ_H 7.98-7.92 (m, 2 H, Phth), 7.83-7.74 (m, 2 H Phth), 7.42-7.12 (m, 4 H, ArH), 6.01 (d, *J* 10.8 Hz, 1 H, β-H), 5.50 (d, *J* 10.8 Hz, 1 H, α-H), 3.56 (s, 3 H, OMe), 2.31 (s, 3 H, Me); **148b** δ_H 7.74-7.62 (m, 4 H, Phth), 7.42-7.12 (m, 4 H, ArH), 5.93 (d, *J* 10.5 Hz, 1 H, β-H), 5.59 (d, *J* 10.5 Hz, 1 H, α-H), 3.81 (s, 3 H, OMe), 2.18 (s, 3 H, Me). The mixture was chromatographed on silica (CH_2Cl_2 / hexane, 9:1) affording *N*-phthaloyl-*p*-bromomethylphenylalanine methyl ester **149** as a colourless oil (1.2 mg, 30%). ν_{max}(neat)/cm^{-1} 2950, 2920, 2850, 1775, 1745, 1725, 1470, 1390, 1245, 1110, 1020, 885, 720; *m/z* (%) 402 (M–H, 17%), 400 (M–H, 17), 322 (38), 299 (38), 277 (32), 262 (32), 256 (34), 254 (34), 249 (45), 218 (40), 175 (100), 130 (34), 104 (76), 76 (52); *m/z* 400.018 (M–H) [Calc. for $C_{19}H_{15}NO_4{}^{79}Br$ (M–H) *m/z* 400.018]. The β-bromides **148a** and **148b** were not isolated, and were identified by comparison of their ^{1}H NMR spectra data obtained from the crude reaction mixture with those of the corresponding bromophenylalanine derivatives **18a**, **18b**, **25** and **28**, as described in Chapter 5 of the Results and Discussion of this thesis.

Treatment of *N-tert*-Butyl-N^{α}-phthaloyl-*p*-methylphenylalaninamide 94 with NBS.

N-tert-Butyl-N^{α}-phthaloyl-*p*-methylphenylalaninamide **94** (5.9 mg, 16.2 μmol) was dissolved in carbon tetrachloride (3 ml), then NBS (2.1 mg, 11.8 μmol) was added and the mixture was heated at reflux for 30 mins. under a nitrogen atmosphere, whilst irradiating with a 300 W sunlamp. The resultant solution was allowed to cool to room temperature, then was washed with water and dried, then concentrated under reduced pressure. The crude mixture was analysed using ^{1}H NMR spectroscopy, which showed the *p*-bromomethylphenylalanine derivative **151**, a 1:1 mixture of diastereomers of the

β-bromides **150a** and **150b**, and the amide **94** in the ratio *ca.* 1.4 : 1.0 : 4.5. **151** δ_H 7.81-7.68 (m, 4 H, Phth), 7.22 (d, *J* 8.1 Hz, 2 H, ArH), 7.15 (d, *J* 8.1 Hz, 2 H, ArH), 5.82 (br s, 1 H, NH), 4.96 (dd, *J* 6.6, 9.9 Hz, 1 H, α-H), 4.38 (s, 2 H CH_2Br), 3.57 (dd, *J* 6.6, 14.7 Hz, 1 H, β-H), 3.43 (dd, *J* 9.9, 14.7 Hz, 1 H, β-H'), 1.31 (s, 9 H, CMe_3); **150a** δ_H 7.96-7.73 (m, 4 H, Phth), 7.07-6.98 (m, 4 H, ArH), 6.17 (d, *J* 11.4 Hz, 1 H, β-H), 5.78 (br s, 1 H, NH), 5.22 (d, *J* 11.4 Hz, 1 H, α-H), 2.19 (s, 3 H, Me), 1.03 (s, 9 H, CMe_3); **150b** δ_H 7.72-7.62 (m, 2 H, Phth), 7.24-7.14 (m, 4 H, ArH), 6.41 (br s, 1 H, NH), 6.05 (d, *J* 11.4 Hz, 1 H, β-H), 5.31 (d, *J* 11.4 Hz, 1 H, α-H), 2.37 (s, 3 H, Me), 1.40 (s, 9 H, CMe_3). The bromides **150a**, **150b** and **151** were inseparable using chromatography on silica, and were therefore identified by comparison of the ^{1}H NMR spectral data obtained from the mixture of regioisomers with those of the corresponding bromophenylalanine derivatives **20a**, **20b**, **31a** and **31b** and the ester **149**.

Competitive Reactions of the Valine Derivatives 95 and 96 with NBS

The relative rates of reactions of the valine derivatives **95** and **96** with NBS were carried out as described above for the competitive reactions of the phenylalanine derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b**, by treating approximately equimolar amounts of each substrate **95** and **96** in carbon tetrachloride with NBS (*ca.* 1.0 equiv.) at reflux in the presence of *tert*-butylbenzamide (*ca.* 0.1 equiv.) as an internal standard whilst photolysing with a 300 W sunlamp. The data obtained from these experiments are summarised in Appendix 13.

Competitive Reactions of the *p*-Methylphenylalanine Derivatives 93 and 94 and *tert*-Butyltoluene with NBS

The relative rates of reactions of the methylphenylalanine derivatives **93** and **94**, at the β-position and at the *p*-methyl substituent, and *tert*-butyltoluene with NBS were determined as described above for the competitive reactions of the phenylalanine derivatives **17**, **19**, **78a**, **78b**, **79a** and **79b**, by treating an approximately equimolar amount of the substrates **93** and **94** and *tert*-butyltoluene in carbon tetrachloride with NBS (*ca.* 1.0 equiv.) in the presence of *tert*-butylbenzamide (*ca.* 0.1 equiv.) as an internal standard, whilst irradiating with a 300 W sunlamp. The data obtained from these experiments are summarised in Appendix 14.

***N*-Bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-methylphenylalaninamide 144**

The title compound **144** was prepared from *N*-*tert*-butyl-N^{α}-phthaloyl-*p*-methylphenylalaninamide **94** (2.5 mg, 6.9 μmol) by treatment with a solution of *tert*-butyl hypobromite (5 ml, 0.4 M), using the procedure described above for the preparation of the *N*-bromophenylalanine derivative **92**. δ_H 7.80-7.76 (m, 2 H, Phth), 7.71-7.67 (m, 2 H, Phth), 7.10 (br d, *J* 8.0 Hz, 2 H, ArH), 6.99 (br d, *J* 8.0 Hz, 2 H, ArH), 5.66 (dd, *J* 5.0, 10.8 Hz, 1 H, α-H), 3.57 (dd, *J* 10.8, 14.2 Hz, 1 H, β-H), 3.47 (dd, *J* 5.0, 14.2 Hz, 1 H, β-H'), 2.23 (s, 3 H, Me), 1.47 (s, 9 H, CMe_3). The crude material was used without further purification or characterisation.

Photolysis of *N*-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-methylphenylalanin-amide 144 in the Presence of *p*-*tert*-Butyltoluene

A solution of the crude *N*-bromoamide **144** at a concentration of approximately 1.6 mM and *p*-*tert*-butyltoluene (*ca.* 1.4 equiv.) in carbon tetrachloride (3 ml) at reflux under an atmosphere of nitrogen was photolysed for 5 mins with a 300 W sunlamp. The solution was concentrated under reduced pressure, then analysed using ^{1}H NMR spectroscopy, which showed the presence of a 1:1 mixture of the β-bromides **150a** and **150b**, the bromide **151** and *p*-*tert*-butylbenzyl bromide in the ratio *ca.* 44:1:3.5.

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Appendix 1

Pergamon

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Neighbouring Group Effects Promote Substitution Reactions over Elimination and Provide a Stereocontrolled Route to Chloramphenicol

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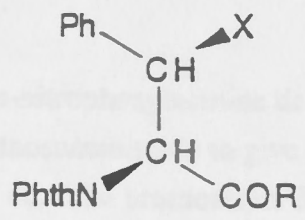
Abstract: In reactions of β-brominated valine and *p*-nitrophenylalanine derivatives to give β-hydroxy amino acid derivatives the carboxyl group, when protected as an amide, exerts a neighbouring group effect to facilitate the substitution process, and reduce competing elimination reactions. As a consequence of the effect, the (2*R*,3*R*)- and (2*R*,3*S*)-stereoisomers of 3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide both react to give (2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, providing a stereoconvergent route to chloramphenicol.

INTRODUCTION

Neighbouring group participation by amido and aminocarbonyl substituents is well known[1] and the chemical and biochemical implications of this phenomenon in reactions of amino acid derivatives have attracted considerable attention.[2-6] For example, it appears that the biochemistry of asparagine incorporated in peptides is influenced by the interaction of the side chain aminocarbonyl moiety with the peptide bonds,[2] while amides derived from either the amino[3,4] or carboxyl group[5] of an amino acid are known to be able to act as nucleophiles or provide anchimeric assistance in solvolysis reactions, *via* 1,5-participation. Recently we reported[7] much greater diastereoselectivity in the synthesis of the hydroxyamides **1d** and **2d** from the bromoamides **1c** and **2c** than in the conversion of the corresponding bromoesters **1a** and **2a** to the hydroxyesters **1b** and **2b**. The enhanced stereoselectivity was attributed to neighbouring group participation by the aminocarbonyl substituent in the reactions of the bromides **1c** and **2c**. Consistent with this proposal, the extent of anchimeric assistance displayed by amides is known to be larger than that shown by esters,[6] although 1,4-participation by amides appears to be unusual. We now report reactions of the bromides **3a,c-5a,c**, in which it is apparent that the neighbouring group effect changes the course of reaction, favouring substitution over elimination, as well as controlling the stereochemistry in the conversion of the bromides **3a,c** and **4a,c** to the alcohols **3b,d** and **4b,d**.

During the course of the present work a stereospecific route to chloramphenicol **6** was also developed. The industrial synthesis of this broad spectrum antibiotic involves the condensation of benzaldehyde with β-nitroethanol[8] but a disadvantage of that and other approaches[9] is that they involve the formation of racemic products which need to be resolved. An asymmetric synthesis based on azide ring-opening of the epoxide **7** has been reported.[10] Alternatively, (*S*)-phenylalanine has been used to obtain the chloramphenicol precursor **9**



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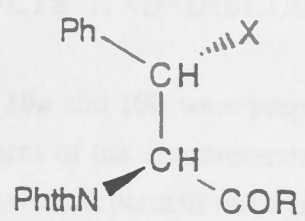

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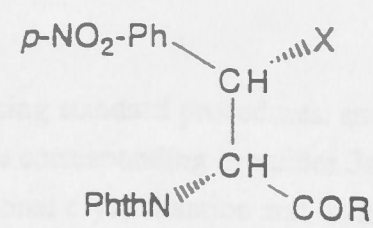

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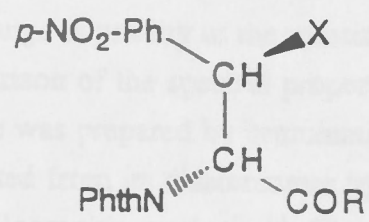

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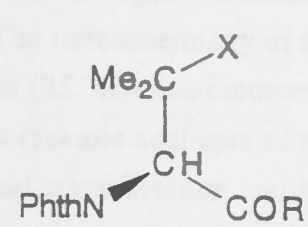

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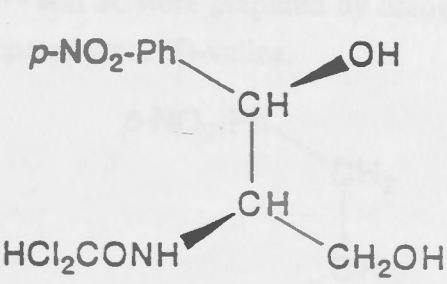
a) X = Br, R = OMe
b) X = OH, R = OMe
c) X = Br, R = $NHCMe_3$
d) X = OH, R = $NHCMe_3$

in a multi-step synthesis (Scheme 1), in which diastereocontrol was achieved by utilising 1,5-neighbouring group participation in the hydrolytic rearrangement of the benzamide 8.[4]



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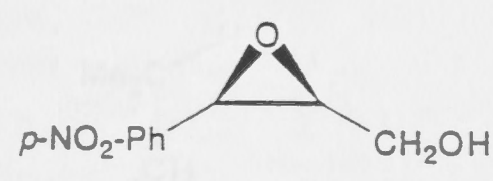

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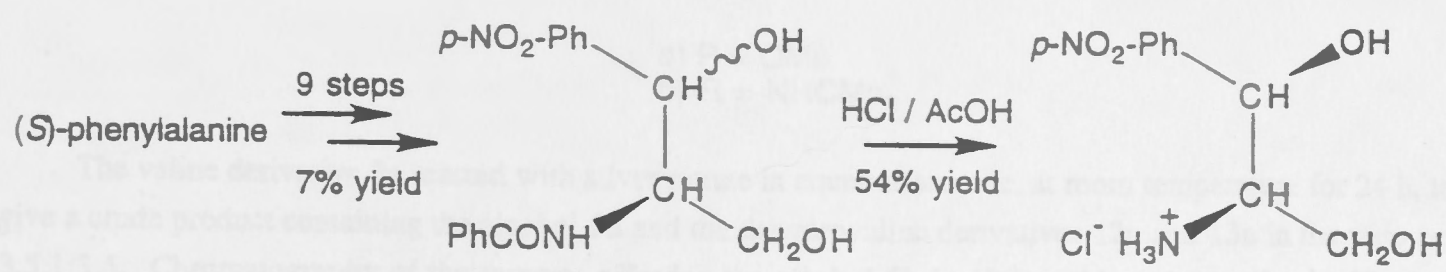
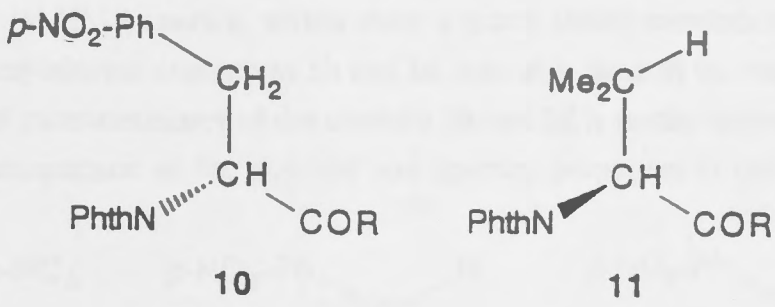


8 9

Scheme 1

RESULTS AND DISCUSSION

The *p*-nitrophenylalanine derivatives **10a** and **10b** were prepared using standard procedures, and treated with *N*-bromosuccinimide to give 1:1 mixtures of the diastereomers of the corresponding bromides **3a** and **4a**, and **3c** and **4c**. The bromoesters **3a** and **4a** were separated through fractional crystallisation and their relative stereochemistry was determined through X-ray crystallographic analysis of the (2*S*,3*R*)-diastereomer **4a**.[11] [Note that the Cahn-Ingold-Prelog designation at the α-carbon of the bromides **3a,c-5a,c** is reversed by comparison with that of the corresponding non-halogenated amino acid derivatives **10a,b** and **11a,b**, due to the change in priority of the substituents.] The stereochemistry of the bromoamides **3c** and **4c** was assigned by comparison of the spectral properties of the (2*S*,3*R*)-diastereomer **4c** with those of a racemic sample. That sample was prepared by bromination of the racemic analogue of the nitrophenylalanine derivative **10b**, then separated from its diastereomer by fractional crystallisation and its structure was determined through X-ray crystallographic analysis.[11] The ^{1}H NMR spectra of the bromides **3a,c** and **4a,c** show the same trends as previously observed with the corresponding phenylalanine derivatives **1a,c** and **2a,c**.[7] The signals corresponding to the carboxyl protecting groups occur at lower chemical shift for the (2*S*,3*S*)-diastereomers **3a** and **3c** than for the corresponding (2*S*,3*R*)-diastereomers **4a** and **4c**, while the (2*S*,3*S*)-diastereomers **3a** and **3c** exhibit the β-proton signal at higher chemical shift, the α-proton at lower chemical shift, and a larger coupling constant between the α- and β-protons, than for the corresponding (2*S*,3*R*)-diastereomers **4a** and **4c**. The bromides **5a**[12] and **5c** were prepared by halogenation of the amino acid derivatives **11a** and **11b**, which had each been prepared from (*S*)-valine.



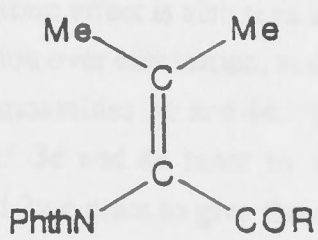
10 **11**

a) R = OMe
b) R = $NHCMe_3$

The valine derivative **5a** reacted with silver nitrate in aqueous acetone, at room temperature for 24 h, to give a crude product containing the alcohol **5b** and the dehydrovaline derivatives **12a** and **13a** in the ratio *ca.* 3.5:1:3.5. Chromatography of the mixture afforded the alcohol **5b** in 43% yield, and the alkenes **12a** and **13a**, in yields of 8 and 34%, respectively. The corresponding reaction of the valinamide **5c** afforded a *ca.* 2:1 mixture of the alcohol **5d** and the alkene **13b**, from which the components were isolated in 63 and 26% yield, respectively. The ^{1}H NMR spectrum of the crude product of the reaction of the valinamide **5c** showed no indication of formation of the alkene **12b**.

The *p*-nitrophenylalanine derivatives **3a,c** and **4a,c** required more vigorous conditions to react. On one occasion, treatment of the bromoester **4a** at 65 °C for 48 h gave the alcohol **3b** in 63% yield, with the dehydrophenylalanine derivatives **14a** and **15a** also being isolated as a 2:3 mixture in 25% yield. Repeated experiments afforded the alcohol **3b** in only 10-30% yield, with higher proportions of the alkenes **14a** and

15a. Under similar conditions, the bromide **3a** gave only the alkene **15a**, in 84% yield, and neither the alcohol **3b** nor the alkene **14a** were detected in the crude product. The analogous reaction of a 1:1 mixture of the bromides **3a** and **4a** carried out using silver sulfate, in place of the nitrate salt, gave mainly the alkene **15a** and only small quantities of either the (*E*)-isomer **14a** or the alcohol **3b**. In contrast, treatment of a 1:1 mixture of



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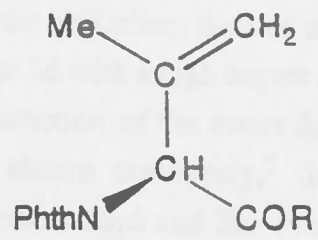
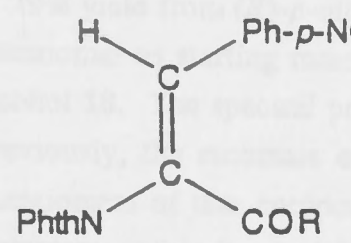


13

a) R = OMe
b) R = $NHCMe_3$

the bromoamides **3c** and **4c** with silver sulfate over 3 days under similar conditions gave only the substitution product **3d** in 64% yield. Reaction of the bromoamides **3c** and **4c** using silver nitrate was complicated by competing formation of a second product, which was tentatively identified as the nitrate **16**. There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^{1}H NMR spectra of the crude products obtained from these reactions of the bromoamides **3c** and **4c**.

The stereochemistry of the dehydrophenylalanine derivatives **14a** and **15a** was assigned on the basis of their ^{1}H NMR spectra, in which the resonance due to the vinylic proton of the (*E*)-isomer **14a** was observed at δ 7.28, 0.85 ppm upfield from that of the corresponding signal for the (*Z*)-alkene **15a**. This is consistent with the general trend displayed by dehydrophenylalanine derivatives.[13] The stereochemistry of the alcohols **3b** and **3d** is apparent from their ^{1}H NMR spectra, which show a much closer correlation with the spectra of the corresponding hydroxyphenylalanine derivatives **1b** and **1d** than with those of the respective diastereomers **2b** and **2d**. The assignment of stereochemistry of the alcohols **3b** and **3d** is further supported by hydrolysis to the free amino acid **18** and comparison of the physical and spectral properties of that material with literature data.[14-16]



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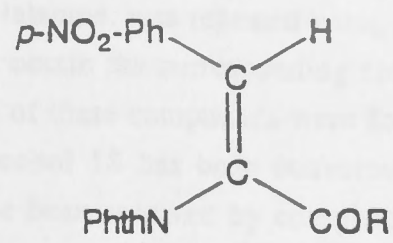

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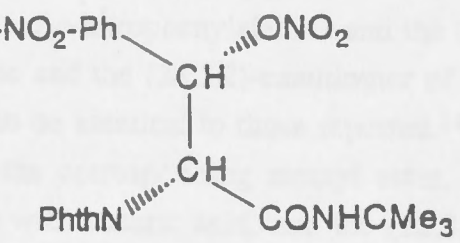
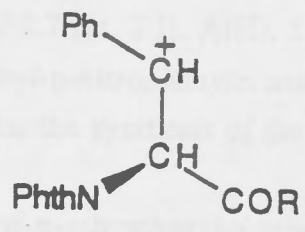


16

a) R = OMe
b) R = $NHCMe_3$

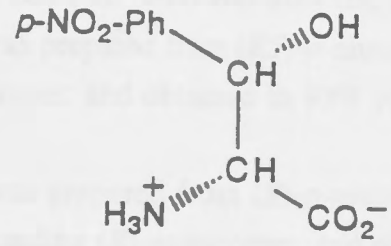
Elimination reactions of the bromovalinate **5a**, to give the alkenes **12a** and **13a**, compete with the substitution reaction, to give the alcohol **5b**. By comparison, the reaction of the bromovalinamide **5c** gives a better yield of the substitution product **5d**. This is not merely a steric effect of the bulky aminocarbonyl substituent to retard elimination. Under these circumstances, the amide **5c** would be expected to react more slowly than the ester **5a**, whereas in competitive experiments the opposite was observed, with the amide **5c**

reacting *ca.* six times faster than the ester **5a**. Instead, the effect of the aminocarbonyl substituent to promote substitution over elimination, and increase the rate of reaction of the bromide **5c**, indicates a neighbouring group effect of the protected carboxyl group to stabilise the carbocation intermediate in the substitution reaction. The neighbouring group effect is also seen in the reactions of the nitrophenylalanine derivatives **3a,c** and **4a,c**, to promote substitution over elimination, and to give the alcohol **3d** with a high degree of stereocontrol from the reaction of the bromoamides **3c** and **4c**. The predominant reaction of the esters **3a** and **4a** is elimination, whereas the amides **3c** and **4c** react by substitution. As shown previously,[7] the bromophenylalanine derivatives **1a,c** and **2a,c** react to give the corresponding alcohols **1b,d** and **2b**. Presumably, in the absense of an electron withdrawing group on the aromatic ring, the carbocations **17a,b** form in the substitution reactions without competing elimination. In that case the only effect of the neighbouring group is to enhance the stereoselectivity in the production of the alcohols **1b,d** and **2b**. The nitrophenylalanine derivatives **3a** and **4a** react predominantly by elimination. When the carboxyl group is protected as an amide, however, the destabilising effect of the nitro substituent on the intermediate carbocation is diminished to the extent that substitution now becomes the favoured reaction pathway.



17

a) R = OMe
b) R = $NHCMe_3$



18

On treament with hydrochloric acid in aqueous acetic acid, the hydroxynitrophenylalanine derivative **3d** hydrolysed to the corresponding free amino acid **18**. The synthetic procedure used to prepare the alcohol **18**, in 29% yield from (*R*)-*p*-nitrophenylalanine, was repeated using racemic *p*-nitrophenylalanine and the (*S*)-enantiomer as starting materials, to obtain the corresponding racemate and the (2*S*,3*R*)-enantiomer of the alcohol **18**. The spectral properties of these compounds were found to be identical to those reported.[14-16] Previously, the racemate of the alcohol **18** has been converted to the corresponding methyl ester, the enantiomers of that compound have been resolved by complexation with tartaric acid, and the (2*S*,3*R*)-stereoisomer has been elaborated to chloramphenicol **6**.[16] Now stereocontrolled access to the (2*S*,3*R*)-enantiomer of the alcohol **18**, as a consequence of neighbouring group participation by an aminocarbonyl substituent to facilitate substitution over elimination and control the stereochemistry of the former, offers a more direct route for synthesis of the antibiotic **6**.

EXPERIMENTAL

General. M.p.s were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded as nujol mulls, liquid films or as solutions in chloroform, on a Hitachi 270-30 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a Bruker ACP-300 or a GEMINI 300

spectrometer, in $CDCl_3$ with Me_4Si as the internal standard, unless otherwise stated. Electron impact (ei) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Fast atom bombardment (fab) mass spectra were recorded on a VG ZAB 2HF spectrometer. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Microanalyses were performed by Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia. Chromatography was performed on Merck-Keiselgel 60 (230-400 mesh ASTM), using ethyl acetate and light petroleum (b.p. 66-68 °C) as eluants. Organic solutions were dried over $MgSO_4$.

All solvents were purified and dried using standard methods. (*S*)-Valine, (*RS*)-*p*-nitrophenylalanine, and (*S*)- and (*R*)-*p*-nitrophenylalanine were purchased from Sigma Chemical Co.

(R)-N-Phthaloyl-p-nitrophenylalanine. A mixture of (*R*)-*p*-nitrophenylalanine monohydrate (1.78 g, 7.81 mmol), phthalic anhydride (1.27 g, 8.58 mmol) and triethylamine (1.1 cm^3, 7.95 mmol) was heated at reflux in toluene (60 cm^3) for 3 h, during which time water was continuously removed using a Dean-Stark condenser. The resultant mixture was cooled in an ice bath and then it was concentrated under reduced pressure. The residue dissolved in dichloromethane and the solution was washed with dilute aqueous hydrochloric acid and water, then it was dried and concentrated under reduced pressure. Crystallisation of the solid residue from a mixture of ethyl acetate and light petroleum yielded the title compound as a pale yellow crystalline solid (2.57 g, 97%), m.p. 203-207 °C; $[\alpha]_{578}^{25}$ +234.5° (c, 0.31 in MeOH); δ_H 8.09 (d, *J* 8.7 Hz, 2 H, ArH), 7.72-7.83 (m, 4 H, phth), 7.36 (d, *J* 8.7 Hz, 2 H, ArH), 5.26 (dd, *J* 7.3 and 9.2 Hz, 1 H, α-H) and 3.72 (m, 2 H, β-H).

(RS)-N-Phthaloyl-p-nitrophenylalanine. This compound was prepared from (*RS*)-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding (*R*)-isomer, and obtained in 93% yield, m.p. 185-187 °C.

(S)-N-Phthaloyl-p-nitrophenylalanine. This compound was prepared from (*S*)-*p*-nitrophenylalanine monohydrate, as described above for the synthesis of the corresponding (*R*)-enantiomer, and obtained in 57% yield, m.p. 200-202 °C (lit.[17] 204.7 °C); $[\alpha]_{578}^{19}$ -230.2° (c, 0.086 in MeOH) (lit.[17] -232.5° (c, 1.55 in MeOH)).

(R)-N-Phthaloyl-p-nitrophenylalanine Methyl Ester **10a.** (*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine (2.50 g, 7.35 mmol) was dissolved in dry methanol (50 cm^3) which had been pretreated with thionyl chloride (400 mg, 3.36 mmol). The solution was stirred under anhydrous conditions for 16 h, then it was concentrated under reduced pressure. The residue dissolved in dichloromethane, and the solution was washed with aqueous sodium carbonate and water, then it was dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the title compound **10a** as a colourless solid (2.24 g, 86%), m.p. 121-122 °C; ν_{max}/cm^{-1} 1775, 1750, 1715, 1600, 1520, 1390, 1345, 1240, 860 and 720; δ_H 8.06 (d, *J* 8.6 Hz, 2 H, ArH), 7.72-7.82 (m, 4 H, phth), 7.45 (d, *J* 8.6 Hz, 2 H, ArH), 5.31 (dd, *J* 5.5 and 10.9 Hz, 1 H, α-H), 3.81 (s, 3 H, OMe), 3.77 (dd, *J* 5.5 and 14.3 Hz, 1 H, β-H) and 3.71 (dd, *J* 10.9 and 14.3 Hz, 1 H, β'-H); *m/z* (ei) (%) 354 (M^+, 12), 295 (37), 278 (14), 218 (36), 207 (100), 190 (37), 176 (25), 130 (33), 104 (17) and 76 (21).

(2S,3S)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester **3a** *and (2S,3R)-3-Bromo-N-phthaloyl-p-nitrophenylalanine Methyl Ester* **4a.** To a solution of (*R*)-*N*-phthaloyl-*p*-nitrophenylalanine methyl ester **10a** (2.20 g, 6.21 mmol) in carbon tetrachloride (40 cm^3), *N*-bromosuccinimide (1.20 g, 6.74 mmol) was added

and the mixture was heated at reflux for 4 h, while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool, before it was filtered. The filtrate was washed with water and dried, then it was concentrated under reduced pressure, to give a 1:1 mixture of the title compounds **3a** and **4a** as a colourless solid (2.69 g, 100%). Fractional recrystallisation of the mixture from a combination of dichloromethane and light petroleum gave the (2*S*,3*S*)-bromide **3a** (1.17 g, 43%), m.p. 198-201 °C; ν_{max}/cm^{-1} 1775, 1750, 1720, 1600, 1525, 1340, 1215, 1100, 820 and 715; δ_H 8.27 (d, *J* 8.8 Hz, 2 H, ArH), 7.82-7.99 (m, 4 H, phth), 7.78 (d, *J* 8.8 Hz, 2 H, ArH), 6.02 (d, *J* 11.2 Hz, 1 H, β-H), 5.51 (d, *J* 11.2 Hz, 1 H, α-H) and 3.59 (s, 3 H, OMe); *m/z* (ei) (%) 434/432 (M^+, 2), 375 (6), 373 (6), 353 (4), 352 (9), 321 (6), 294 (29), 293 (17), 287 (10), 285 (10), 247 (7), 219 (16), 218 (100), 190 (30), 130 (18), 104 (40) and 76 (37) (Found: C, 49.8; H, 3.0; N, 6.5. Calc. for $C_{18}H_{13}BrN_2O_6$: C, 49.9; H, 3.0; N, 6.5%). Further recrystallisation gave the (2*S*,3*R*)-bromide **4a** (1.07 g, 40%), m.p. 195-197 °C; ν_{max}/cm^{-1} 1775, 1755, 1720, 1605, 1525, 1390, 1350, 855 and 720; δ_H 8.07 (d, *J* 8.7 Hz, 2 H, ArH), 7.68-7.76 (m, 4 H, phth), 7.56 (d, *J* 8.7 Hz, 2 H, ArH), 5.97 (d, *J* 10.3 Hz, 1 H, β-H), 5.59 (d, *J* 10.3 Hz, 1 H, α-H) and 3.83 (s, 3 H, OMe); *m/z* (ei) (%) 434/432 (M^+, 1), 375 (3), 373 (3), 353 (6), 352 (3), 321 (7), 294 (20), 293 (12), 287 (3), 285 (3), 247 (5), 219 (15), 218 (100), 190 (29), 130 (16), 104 (28) and 76 (26) (Found: C, 49.8; H, 3.0; N, 6.6. Calc. for $C_{18}H_{13}BrN_2O_6$: C, 49.9; H, 3.0; N, 6.5%). The structure of the bromide **4a** was confirmed through X-ray crystallographic analysis.[11]

*(RS)-*N*-tert-Butyl-*N$^{\alpha}$*-phthaloyl-*p*-nitrophenylalaninamide.* To a suspension of (*RS*)-*N*-phthaloyl-*p*-nitrophenylalanine (2.00 g, 5.88 mmol) in dichloromethane (40 cm^3), triethylamine (0.81 cm^3, 5.85 mmol) was added. The resultant solution was cooled to 0 °C, then ethyl chloroformate (0.56 cm^3, 5.86 mmol) was added. That mixture was stirred for 10 min, then *tert*-butylamine (0.61 cm^3, 5.85 mmol) was added and the solution was warmed to room temperature. After stirring for a further 30 min, the mixture was filtered and the filtrate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water, then it was dried and concentrated under reduced pressure. The residue was chromatographed to give the title compound, as a colourless crystalline solid after recrystallisation from a mixture of ethyl acetate and light petroleum (1.26 g, 54%), m.p. 215-216 °C, ν_{max}/cm^{-1} 3316, 2920, 2848, 1774, 1714, 1658, 1554, 1516, 1456, 1382, 1344, 1220, 1088, 1016, 888, 874, 766 and 726; δ_H 8.03 (d, *J* 8.6 Hz, 2 H, ArH), 7.77-7.69 (m, 4 H, phth), 7.33 (d, *J* 8.6 Hz, 2 H, ArH), 5.93 (br s, 1 H, NH), 5.02 (t, *J* 8.4 Hz, 1 H, α-H), 3.65 (d, *J* 8.4 Hz, 2 H, β-H) and 1.33 (s, 9 H, CMe_3); δ_C 29.1, 35.2, 52.4, 56.4, 124.2, 124.3, 130.3, 131.6, 135.1, 145.4, 147.4, 167.1 and 168.3; *m/z* (ei) (%) 395 (M^+, 5), 352 (5), 341 (10), 256 (20), 236 (5) and 213 (10) (Found: C, 63.6; H, 5.3; N, 10.5. Calc. for $C_{21}H_{21}N_3O_5$: C, 63.8; H, 5.3; N, 10.6%).

*(R)-*N*-tert-Butyl-*N$^{\alpha}$*-phthaloyl-*p*-nitrophenylalaninamide* **10b.** This compound was prepared from (*R*)-*N*-phthaloyl-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 72% yield, m.p. 230 °C (dec.); $[\alpha]_D^{25}$ +117.0° (c, 0.227 in $CHCl_3$).

*(S)-*N*-tert-Butyl-*N$^{\alpha}$*-phthaloyl-*p*-nitrophenylalaninamide.* This compound was prepared from (*S*)-*N*-phthaloyl-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 79% yield, m.p. 230 °C (dec.); $[\alpha]_D^{21}$ -120.8° (c, 0.418 in $CHCl_3$).

*(2RS,3RS)-3-Bromo-*N*-tert-butyl-*N$^{\alpha}$*-phthaloyl-*p*-nitrophenylalaninamide and (2RS,3SR)-3-Bromo-*N*-tert-butyl-*N$^{\alpha}$*-phthaloyl-*p*-nitrophenylalaninamide.* To a solution of (*RS*)-*N-tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide (771 mg, 1.95 mmol) in a mixture of carbon tetrachloride and dichloromethane (4:1, 50

cm^3), *N*-bromosuccinimide (695 mg, 3.90 mmol) was added and the mixture was heated at reflux for 3 h, while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool, before it was filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give a 1:1 mixture of the title compounds as a colourless solid (905 mg, 98%), m.p. 194-210 °C; ν_{max}/cm^{-1} 3380, 3350, 2950, 2920, 2850, 1775, 1715, 1670, 1520, 1460, 1380, 1350, 1280, 1220, 1110, 1090, 1060, 880, 720 and 700; *m/z* (fab) (%) 476/474 ($M+H^+$, 40%), 420/418 (20), 295 (30), 154 (100) and 136 (90) (Found: C, 53.1; H, 4.2; N, 8.9. Calc. for $C_{21}H_{20}BrN_3O_5$: C, 53.2; H, 4.3; N, 8.9%). Fractional recrystallisation of the mixture of isomers from a combination of dichloromethane and light petroleum afforded a sample of (2*RS*,3*SR*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, δ_H 8.08 (d, *J* 8.9 Hz, 2 H, ArH), 7.79-7.64 (m, 4 H, phth), 7.56 (d, *J* 8.9 Hz, 2 H, ArH), 6.23 (br s, 1 H, NH), 6.18 (d, *J* 11.4 Hz, 1 H, β-H), 5.29 (d, *J* 11.4 Hz, 1 H, α-H) and 1.41 (s, 9 H, CMe_3); δ_C 29.1, 46.4, 52.9, 60.7, 124.3, 124.5, 129.3, 129.4, 131.2, 135.1, 145.3, 164.8 and 167.5. The structure of this material was confirmed through X-ray crystallographic analysis.[11] The ^1H and ^{13}C NMR spectra of the mixture of diastereomers showed resonances for the (2*RS*,3*RS*)-isomer, δ_H 8.26 (d, *J* 8.9 Hz, 2 H, ArH), 7.98-7.81 (m, 4 H, phth), 7.77 (d, *J* 8.9 Hz, 2 H, ArH), 6.27 (br s, 1 H, NH), 6.20 (d, *J* 11.7 Hz, 1 H, β-H), 5.19 (d, *J* 11.7 Hz, 1 H, α-H) and 1.11 (s, 9 H, CMe_3); δ_C 28.8, 49.1, 52.4, 62.7, 124.5, 124.6, 130.0, 130.1, 131.6, 135.3, 148.3, 163.9 and 168.3.

(2S,3S)-3-Bromo-N-tert-*butyl*-N^{α}-*phthaloyl*-p-*nitrophenylalaninamide* **3c** *and (2S,3R)-3-Bromo*-N-tert-*butyl*-N^{α}-*phthaloyl*-p-*nitrophenylalaninamide* **4c**. A 1:1 mixture of these compounds was prepared from (*R*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 95% yield.

(2R,3R)-3-Bromo-N-tert-*butyl*-N^{α}-*phthaloyl*-p-*nitrophenylalaninamide and (2R,3S)-3-Bromo*-N-tert-*butyl*-N^{α}-*phthaloyl*-p-*nitrophenylalaninamide*. A 1:1 mixture of these compounds was prepared in quantitative yield from (*S*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate.

Treatment of (2S,3S)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester* **3a** *with Silver Nitrate in Aqueous Acetone*. To a solution of the bromide **3a** (50 mg, 0.12 mmol) in acetone (3 cm^3), a solution of silver nitrate (25 mg, 0.15 mmol) in water (2 cm^3) was added. The resultant mixture was stirred at 65 °C in the dark for 48 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane and the organic extracts were dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the (*Z*)-*p*-nitrophenylalanine derivative **15a** as large colourless prisms (34 mg, 84%), m.p. 133-134 °C; ν_{max}/cm^{-1} 1780, 1720, 1600, 1530 and 1345; δ_H 8.16 (d, *J* 8.8 Hz, 2 H, ArH), 8.13 (s, 1 H, β-H), 7.92-7.83 (m, 4 H, phth), 7.55 (d, *J* 8.8 Hz, 2 H, ArH), 3.87 (s, 3 H, OMe); *m/z* (ei) (%) 352 (M^+, 90), 342 (63), 293 (41), 292 (46), 247 (24), 218 (15), 190 (18), 166 (21), 104 (100) and 76 (73); *m/z* (ei) 352.068 (M^+) [Calc. for $C_{18}H_{12}N_2O_6$ (M^+) *m/z* 352.070]. Neither the alcohol **3b** nor the alkene **14a** were detected in the crude product.

Treatment of (2S,3R)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester* **4a** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **4a**, carried out as described above for the reaction of the stereoisomer **3a**, afforded an oil which was chromatographed. Elution afforded a 2:3 mixture of the dehydrophenylalanine derivatives **14a** and **15a** as a viscous oil (25%). The ^1H NMR spectrum of the mixture

showed resonances for the (*Z*)-isomer **15a**, identical to those described above, and signals for the (*E*)-isomer **14a**, δ_H 8.26 (d, *J* 8.7 Hz, 2 H, ArH), 7.80-7.98 (m, 4 H, phth), 7.60 (d, *J* 8.7 Hz, 2 H, ArH), 7.28 (s, 1 H, β-H) and 3.72 (s, 3 H, OMe). Continued elution gave the β-hydroxy-*p*-nitrophenylalanine derivative **3b** as colourless needles (63%), after recrystallisation from a mixture of dichloromethane and light petroleum, m.p. 183-185 °C: ν_{max}/cm^{-1} 3604, 3421, 1779, 1752, 1714, 1614, 1526, 1392, 1352 and 1182; δ_H 8.13 (d, *J* 8.9 Hz, 2 H, ArH), 7.82-7.73 (m, 4 H, phth), 7.54 (d, *J* 8.9 Hz, 2 H, ArH), 5.79 (dd, *J* 4.4 and 10.0 Hz, 1 H, β-H), 5.53 (d, *J* 4.4 Hz, 1 H, α-H), 5.34 (d, *J* 10.0 Hz, 1 H, OH) and 3.89 (s, 3 H, OMe); *m/z* (fab) (%) 371 ($M+H^+$, 9), 353 (3), 321 (3), 307 (11), 289 (9), 219 (3), 154 (100), 137 (66), 136 (79), 107 (28), 89 (33) and 77 (31).

(2RS,3SR)-3-Hydroxy-N-tert-*butyl*-N^{α}-*phthaloyl*-p-*nitrophenylalaninamide*. To a solution of a 1:1 mixture of (2*RS*,3*RS*)-3-bromo-*N-tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide and the (2*RS*,3*SR*)-isomer (265 mg, 0.56 mmol) in acetone (10 cm^3) and water (10 cm^3), silver sulfate (263 mg, 0.84 mmol) was added and the suspension was heated at 65 °C in the dark for 3 days. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue dissolved in dichloromethane and the solution was washed with saturated brine, then it was dried and concentrated under reduced pressure. The residue was chromatographed, to give the title compound as an off-white crystalline solid (154 mg, 67%), m.p. 209-210 °C; ν_{max}/cm^{-1} 3700, 3400, 3160, 3000, 2920, 2270, 1830, 1800, 1720, 1650, 1610, 1570, 1480, 1390 and 1110; δ_H 8.14 (d, *J* 8.8 Hz, 2 H, ArH), 7.81-7.71 (m, 4 H, phth), 7.54 (d, *J* 8.8 Hz, 2 H, ArH), 6.01 (br s, 1 H, NH), 5.68 (dd, *J* 4.9 and 8.3 Hz, 1 H, β-H), 5.17 (d, *J* 4.9 Hz, 1 H, α-H), 4.93 (d, *J* 8.3 Hz, 1 H, OH) and 1.37 (s, 9 H, CMe_3); δ_C 168.6, 164.9, 147.4, 134.7, 131.1, 126.6, 123.9, 123.6, 71.7, 59.9, 52.3 and 28.6; *m/z* (ei) (%) 412 ($M+H^+$, 1), 384 (2), 378 (2), 356 (1), 294 (82), 260 (100) and 204 (30) (Found: C, 61.0; H, 5.3; N, 10.0. Calc. for $C_{21}H_{21}N_3O_6$: C, 61.3; H, 5.2; N, 10.2%).

(2R,3S)-3-Hydroxy-N-tert-*butyl*-N^{α}-*phthaloyl*-p-*nitrophenylalaninamide* **3d**. This compound was prepared from a 1:1 mixture of the bromides **3c** and **4c**, as described above for the synthesis of the corresponding racemate, and obtained in 64% yield, m.p. 226-228 °C; $[\alpha]_D^{25}$ +84.1° (c, 0.453 in $CHCl_3$). There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^1H NMR spectrum of the crude reaction mixture.

(2S,3R)-3-Hydroxy-N-tert-*butyl*-N^{α}-*phthaloyl*-p-*nitrophenylalaninamide*. This compound was prepared from a 1:1 mixture of (2*R*,3*R*)- and (2*R*,3*S*)-3-bromo-*N-tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 62% yield, m.p. 220-222 °C; $[\alpha]_D^{20}$ -83.1 (c, 0.083 in $CHCl_3$).

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester with Silver Sulfate in Aqueous Acetone*. A 1:1 mixture of the title bromides was treated with silver sulfate in aqueous acetone, as described for the reaction of the bromoamides **3c** and **4c**. Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed that the racemate of the alcohol **3a** and the alkenes **14a** and **15a** were present in the ratio *ca.* 1:1:10.

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-tert-*butyl*-N^{α}-*phthaloyl*-p-*nitrophenylalaninamide with Silver Nitrate in Aqueous Acetone*. The reaction of a 1:1 mixture of the title bromides, carried out as

described above for the reaction of the bromoester **3a**. afforded an oil which was chromatographed. Elution afforded the nitrate **16** (19%), m.p. 192 °C (dec.); ν_{max}/cm^{-1} 3720, 3460, 3390, 3190, 3020, 2950, 2290, 1830, 1800, 1740, 1670, 1630, 1550, 1490, 1400, 1370, 1320, 1300, 1240, 1190 and 1110; δ_H 8.30 (d, *J* 8.9 Hz, 2 H, ArH), 7.81-7.92 (m, 4 H, phth), 7.77 (d, *J* 8.9 Hz, 2 H, ArH), 7.19 (d, *J* 10.7 Hz, 1 H, β-H), 5.89 (br s, 1 H, NH), 4.90 (d, *J* 10.7 Hz, 1 H, α-H) and 1.14 (s, 9 H, CMe_3); δ_C 167.6, 163.1, 148.6, 141.8, 134.9, 131.2, 129.1, 124.1, 124.1, 78.1, 57.8, 52.2 and 28.3; *m/z* (ei) (%) 457 ($M+H^+$, 30), 393 (15), 307 (40), 286 (100) and 260 (30). Continued elution gave (2*RS*,3*SR*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (54%), identical to the sample obtained as described above. There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^1H NMR spectrum of the crude product.

*(2RS,3SR)-3-Hydroxy-*p*-nitrophenylalanine*. A mixture of (2*RS*,3*SR*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (85 mg, 0.21 mmol) in a 2:1 mixture of 6N hydrochloric acid and acetic acid (10 cm^3) was heated at reflux for 5 h and stirred overnight at room temperature, before it was concentrated under reduced pressure. Water (10 cm^3) was added to the residue, then the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (10 cm^3) and to that solution aniline (0.7 cm^3) in dichloromethane (10 cm^3) was added. The mixture was let stand at 4 °C for 24 h and the material which crystallised was separated by filtration and washed with dichloromethane, to give the title compound as an off-white powder (27 mg, 58%), m.p. 192-193 °C (lit.[14] 187-188 °C (dec.)); ν_{max}/cm^{-1} 3550, 3200, 2920, 2870, 1610, 1590, 1530, 1460, 1380, 1350, 1200, 1110, 1010, 865, 855, 740 and 710; δ_H (CF_3CO_2D) 8.33 (d, *J* 8.8 Hz, 2 H, ArH), 7.74 (d, *J* 8.8 Hz, 2 H, ArH), 5.77 (d, *J* 3.9 Hz, 1 H, β-H) and 4.70 (d, *J* 3.9 Hz, 1 H, α-H); δ_C (D_2O) 173.5, 149.6, 149.0, 129.1, 126.0, 72.7 and 62.5; *m/z* (fab) (%) 227 ($M+H^+$). The ^1H NMR spectral data for this compound is consistent with that reported.[14]

*(2R,3S)-3-Hydroxy-*p*-nitrophenylalanine* **18**. This compound was prepared from the alcohol **3d**, as described above for the synthesis of the corresponding racemate, and obtained in 69% yield, m.p. 200-203 °C (lit.[15] 174-176 °C); $[\alpha]_D^{25}$ +35.3° (c, 0.102 in 1N HCl) (lit.[15] $[\alpha]_D^{25}$ +27° (c, 0.5 in H_2O)).

*(2S,3R)-3-Hydroxy-*p*-nitrophenylalanine*. This compound was prepared from the (2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 54% yield, m.p. 204-205 °C; $[\alpha]_D^{20}$ -36.4° (c, 0.176 in 1N HCl) (lit.[16] $[\alpha]_D^{21.5}$ -33.8° (c, 5 in 1N HCl)).

*(S)-*N*-tert-Butyl-*N*$^{\alpha}$-phthaloylvalinamide* **11b**. To a suspension of *(S)-N*-phthaloylvaline[12] (15.57 g, 63 mmol) in dichloromethane (60 cm^3), triethylamine (6.37 g, 63 mmol) was added. The resulting solution was cooled to 0 °C, then ethyl chloroformate (6.87 g, 63 mmol) was added and the mixture was stirred for 15 min. *tert*-Butylamine (4.60 g, 63 mmol) was added and the mixture was allowed to warm to room temperature, then it was stirred for a further 40 min. The mixture was filtered and the filtrate was washed with water, then it was dried and concentrated under reduced pressure. A portion (*ca.* 4.6 g, 25%) of the residue was chromatographed, to give the title compound **11b** as a colourless crystalline solid (2.60 g), m.p. 144-147 °C; $[\alpha]_D^{21}$ +32.3° (c, 8.7 in $CHCl_3$); ν_{max}/cm^{-1} 3400, 3365, 2920, 2850, 1760, 1710, 1680, 1550, 1530, 1470, 1400, 1070 and 715; δ_H 7.81-7.91 (m, 4 H, phth), 7.13 (br s, 1 H, NH), 4.35 (d, *J* 11.3 Hz, 1 H, α-H), 2.88 (m, 1 H, β-H), 1.39 (s, 9 H, CMe_3), 1.15 (d, *J* 6.7 Hz, 3 H, CH_3) and 0.87 (d, *J* 6.5 Hz, 3 H, CH_3'); δ_C 21.6, 21.7, 29.8, 30.6, 53.3, 66.7, 125.6, 133.4, 136.3, 169.9 and 170.5; *m/z* (ei) (%) 303 ($M+H^+$, 1), 275

(1), 260 (5) and 202 (100) (Found: C, 67.3; H, 7.6; N, 9.2%. Calc. for $C_{17}H_{22}N_2O_3$: C, 67.5; H, 7.3; N, 9.3%).

*(R)-3-Bromo-*N*-tert-butyl-*N*$^{\alpha}$-phthaloylvalinamide* **5c**. A mixture of *N*-bromosuccinimide (1.18 g, 6.6 mmol) and the amide **11b** (1.33 g, 4.4 mmol) in carbon tetrachloride (60 cm^3) was heated at reflux for 2 h, while it was irradiated with a 250 W mercury lamp. The mixture was then cooled to 0 °C and filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give the title compound **5c** as fine colourless needles, after recrystallisation from a mixture of light petroleum and ether (1.54 g, 92%), m.p. 139-141 °C; $[\alpha]_D^{20}$ +11.6° (c, 3.03 in $CHCl_3$); ν_{max}/cm^{-1} 3380, 2920, 2850, 1710, 1530, 1460, 1380, 1080 and 720; δ_H 7.67 (m, 4 H, phth), 5.28 (s, 1 H, α-H), 2.07 (s, 3 H, CH_3), 1.86 (s, 3 H, CH_3') and 1.30 (s, 9 H, CMe_3); δ_C 30.5, 35.0, 35.4, 54.0, 67.7, 68.1, 125.8, 133.3, 136.6, 166.0 and 170.2; *m/z* (ei) (%) 381/383 ($M+H^+$, 5), 380/382 (5), 279/381 (5), 365/367 (10), 325/327 (15), 308/310 (15) and 301 (100) (Found: C, 53.7; H, 5.5; N, 7.1. Calc. for $C_{17}H_{21}BrN_2O_3$: C, 53.6; H, 5.6; N, 7.3%).

*Treatment of (R)-3-Bromo-*N*-phthaloylvaline Methyl Ester* **5a** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **5a**,[12] carried out at room temperature for 14 h, but otherwise as described above for the reaction of the nitrophenylalanine derivative **3a**, afforded an oil which was chromatographed. Elution gave the α,β-dehydrovaline derivative **12a** (40 mg, 8%), m.p. 81-82 °C; δ_H 7.40-8.10 (m, 4 H, phth), 3.68 (s, 3 H, OMe), 2.43 (s, 3 H, CH_3) and 1.88 (s, 3 H, CH_3') (Found: C, 64.7; H, 5.1; N, 5.4. Calc. for $C_{14}H_{13}NO_4$: C, 64.8; H, 5.1; N, 5.4%). Continued elution afforded the β,γ-dehydrovaline derivative **13a** (0.15 g, 34%); ν_{max}/cm^{-1} 2950, 1780, 1748, 1728, 1470, 1440, 1386, 1293, 1245, 1203, 1113, 915 and 717; δ_H 7.75-7.92 (m, 4 H, phth), 5.38 (br s, 1 H, γ-H), 5.14 (br s, 1 H, γ-H'), 5.11 (s, 1 H, α-H), 3.79 (s, 3 H, OMe) and 1.92 (s, 3 H, β-CH_3); *m/z* (ei) (%) 259 (M^+, 8), 227 (20) and 200 (100). Further elution gave the β-hydroxyvaline derivative **5b** (0.21 g, 43%), m.p. 86-87 °C; ν_{max}/cm^{-1} 3544, 1767, 1725, 1275 and 717; δ_H 7.91-7.80 (m, 4 H, phth), 4.41 (br s, 1 H, OH), 3.77 (s, 3 H, OMe), 1.53 (s, 3 H, CH_3) and 1.31 (s, 3 H, CH_3'); *m/z* (ei) (%) 262 ($M-CH_3^+$, 10), 246 (5), 230 (28), 219 (100), 188 (74), 187 (98) and 160 (74) (Found: C, 60.6; H, 5.5; N, 5.1. Calc. for $C_{14}H_{15}NO_5$: C, 60.6; H, 5.5; N, 5.1%). Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed the alcohol **5b** and the alkenes **12a** and **13a** to be present in the ratio *ca.* 3.5 : 1 : 3.5.

*Treatment of (R)-3-Bromo-*N*-tert-butyl-*N*$^{\alpha}$-phthaloylvalinamide* **5c** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **5c**, carried out as described above for the reaction of the ester **5a**, afforded an oil which was chromatographed. Elution gave the β,γ-dehydrovaline derivative **13b** as a colourless oil (26%); ν_{max}/cm^{-1} 3450, 2975, 2950, 1780, 1710, 1695, 1525, 1460, 1475 and 1385; δ_H 7.89-7.73 (m, 4 H, phth), 6.28 (br s, 1 H, NH), 5.27 (s, 1 H), 5.23 (s, 1H), 5.21 (s, 1H), 1.89 (s, 3 H, CH_3) and 1.43 (s, 9 H, CMe_3); δ_C 169.8, 167.3, 141.6, 136.1, 133.8, 125.4, 119.5, 62.5, 53.7, 30.5 and 22.8; *m/z* (ei) (%) 300 (M^+, 5) and 200 (100) (Found: C, 68.0; H, 7.0; N, 9.0. Calc. for $C_{17}H_{20}N_2O_3$: C, 68.0; H, 6.7; N, 9.3%). Further elution afforded the alcohol **5d**, as colourless crystals after recrystallisation from a mixture of ether and light petroleum (63%), m.p. 135-136 °C; ν_{max}/cm^{-1} 3328, 3084, 2972, 2928, 2248, 1774, 1720, 1660, 1614, 1550, 1470, 1384, 1224, 1176, 1144, 1088, 1048, 992, 956, 912, 878, 788, 774, 724 and 646; δ_H 7.84-7.79 (m, 2 H, phth), 7.73-7.69 (m, 2 H, phth), 7.30 (br s, 1 H, NH), 4.61 (s, 1 H, α-H), 4.25 (br s, 1 H, OH),

1.41 (s, 3 H, CH_3), 1.30 (s, 9 H, CMe_3) and 1.22 (s, 3 H, CH_3); *m/z* (ei) (%) 318 (M^+, 50), 300 (10), 259 (50), 201 (100), 187 (100) and 160 (95) (Found: C, 64.3; H, 7.2; N, 8.7. Calc. for $C_{17}H_{22}N_2O_4$: C, 64.1; H, 7.0; N, 8.8%). The structure of the alcohol **5d** was confirmed through X-ray crystallographic analysis.[11] Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed the alcohol **5d** and the alkene **13b** were present in the ratio *ca.* 2 : 1.

Competitive Hydrolysis Reactions of the Bromides **5a** *and* **5c**. The relative rates of reaction of the bromides **5a** and **5c** with silver nitrate were determined by treating an equimolar ratio of the substrates at a concentration of approximately 0.1 mM in aqueous acetone (1:1, v/v) with the silver salt (1.4 equiv.) at room temperature, in the presence of *N-tert*-butylbenzamide (0.5 equiv.) as an internal standard. Aliquots of the reaction mixture were sampled at intervals and worked up as described for the preparative studies, then analysed by ^1H NMR spectroscopy. Integration of peaks characteristic of the residual bromides **5a** and **5c** and the internal standard, and comparison with the spectra of the corresponding starting mixtures, were used to determine the percentage of each substrate remaining, from which the ratios of the logarithms of those percentages were used to calculate the relative rates of reaction. Relative rates of duplicate experiments varied by less than 10%.

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Appendix 2

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Anchimeric Assistance in Hydrogen Atom Transfer Reactions on the Side Chains of Amino Acid Derivatives

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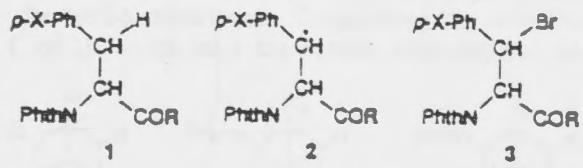
Only a limited range of examples of neighboring group participation in atom transfer reactions have been reported. Anchimeric assistance has been observed in hydrogen atom abstractions, in the vicinal bromination of alkyl bromides,[1,2] and in reactions of *tert*-butoxy radical with Et_4Si, Et_4Ge, and Et_4Sn.[3] Results of studies by Wilt *et al.*,[4] of reactions of β-haloalkylsilanes with stannanes, have also been shown[3] to illustrate neighboring group participation in halogen atom transfer reactions. In each of these systems alkyl radical production is facilitated by a substituent on carbon adjacent to the incipient radical center, through 1,3-participation. We now report strong evidence for anchimeric assistance by an amido substituent, in hydrogen atom transfer reactions, through 1,4-participation. The present work stems from our earlier observations[5] that nucleophilic substitution reactions of **3a**−**f** to give alcohols are substantially affected through neighboring group participation by the ester and amide groups, particularly in the latter case where the amido substituent can interact more extensively with an electron deficient center developing in a reaction transition state.[6] In that work, **3a**−**f** were prepared, each as a 1:1 mixture of the diastereomers, by treatment of **1a**−**f** with NBS. The reverse transformations, of **3a**−**f** to **1a**−**f**, have now been accomplished using Ph_3SnH. As these reactions may be assumed to proceed *via* hydrogen and halogen atom transfer, respectively, to give the corresponding radicals **2a**−**f**, they



(a) X = H, R = OMe
(b) X = H, R = NHt Bu
(c) X = OAc, R = OMe
(d) X = OAc, R = NHt Bu
(e) X = NO_2, R = OMe
(f) X = NO_2, R = NHt Bu

provided the opportunity to probe for anchimeric assistance in atom transfer reactions.

The relative rates of reaction of **1a**−**f** to give **3a**−**f** were determined in standard competitive experiments, by measuring the relative rates of consumption of the starting materials and of formation of the products, and in a similar manner the relative rates of reduction of **3a**−**f** were also determined (Table 1). The effect of the aromatic ring substituents on the reactions of **1a**−**f** is similar to that previously reported for radical bromination of series of substituted toluene derivatives,[7] with **1a** and **1c**, and **1b** and **1d** reacting much faster than the corresponding nitro-substituted analogues **1e** and **1f**, respectively. This is consistent with the transition state proposed for radical bromination, in which hydrogen transfer to electrophilic bromine atom occurs with the development of an electron deficient center at the site of hydrogen abstraction.[7] In the processes involving Ph_3SnH, the relative rates of reaction reflect the ease with which **3a**−**f** transfer a bromine atom to the triphenyltin radical. In these processes, the effect of the nitro substituent is the reverse of that seen in the reactions with NBS, with the nitro-substituted compounds **3e** and **3f** reacting much faster than **3a**−**d**. The relative reactivity of **3a**−**f** is to be expected, however, as the transition state for a reaction of this type involves transfer of the halogen to the nucleophilic stannyl radical with the development of an electron rich center at the site of halogen abstraction.[8]

Table 1. Relative Rates of Reaction[a] of the Amino Acid Derivatives **1a**−**f** and **3a**−**f**

compd	k_{rel}[b]	compd[c]	k_{rel}[d]
1a	8	**3a**	1[e]
1b	40	**3b**	1
1c	9	**3c**	1.2
1d	34	**3d**	1.4
1e	1[e]	**3e**	4
1f	5	**3f**	4

[a] Relative rates of reaction determined in duplicate experiments varied by less than 20%. [b] Reaction with NBS in CCl_4 at reflux under N_2, initiated using a 250 W mercury lamp. [c] Data refers to reaction of the *threo* diastereomer in each case. The diastereoselectivity was less than 1.1 in the reactions of **3a**, **3b**, and **3e** and low in the reactions of **3c**, **3d**, and **3f**, but not possible to accurately quantify in the latter cases due to decomposition of the *erythro* isomers. [d] Reaction with Ph_3SnH in benzene at reflux under N_2, initiated using either AIBN or a 250 W mercury lamp. [e] Assigned as unity within each column.

Whether the carboxyl group is protected as an ester or an amide has very little effect on the relative rates of reaction of **3a**−**f** with Ph_3SnH, yet in the reactions with NBS, each of the amides **1b**, **1d**, and **1f** reacted approximately 5 times faster than the corresponding ester **1a**, **1c**, and **1e**, respectively. These effects are not consistent with steric constraints resulting from the greater bulk of the amido substituent relative to the ester group, as such factors would be expected to be at least as severe in the reactions of **3a**−**f**, where the large bromine atom is transferred to the bulky triphenyltin radical. The most obvious interpretation of the results is that the amido substituent of **1b**, **1d**, and **1f**, being more electron rich than the ester group of **1a**, **1c**, and **1e**, facilitates reaction by interacting directly with the electron deficient center in the bromination transition state (Figure 1). The analogous effect would not be expected in the reactions of **3a**−**f**, where any interaction between the carboxyl group and the electron rich center developing in the transition state would be unfavorable and would therefore be avoided.

Consistent with this interpretation, there was little diastereoselectivity in the reactions of **3a**−**f** with Ph_3SnH, indicating that the energetics of these processes are little affected by geometrical constraints on interactions between substituents. To examine the possibility of stereoselectivity in the hydrogen transfer

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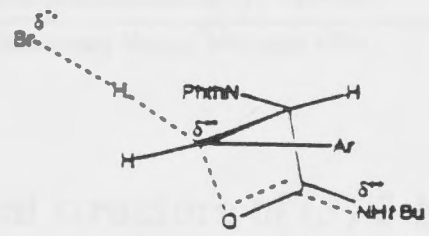
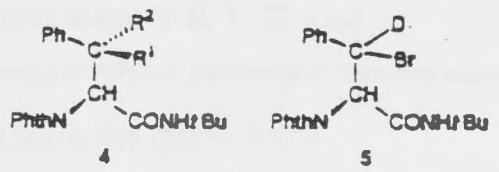


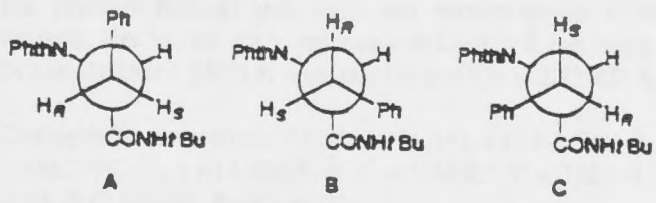
Figure 1. Neighboring group participation by the amido group in the reactions to give the radicals 2b, 2d, and 2f.

reactions, the deuterides **4a** and **4b**[9] were treated with NBS. The (2*S*,3*S*)-deuteride **4a** gave a 1:1 mixture of the diastereomers of **5**, with each diastereomer containing 79% deuterium, whereas the diastereomer **4b** gave **5**, with 66% deuterium retention.



(a) $R^1 = H$, $R^2 = D$
(b) $R^1 = D$, $R^2 = H$

These results correlate with a deuterium isotope effect of 2.7 for the hydrogen atom transfer[10] and a stereoselectivity of 1.4 for abstraction of the pro-*R* hydrogen. This selectivity is not simply a result of steric effects. The ^{1}H NMR spectra of **4a** and **4b** and the respective coupling constants, $J_{\alpha,\beta}$, of 9.8 and 5.8 Hz indicate that the preferred conformation of the *S*-enantiomer of **1b** is **A**. This is the only staggered conformation which will give rise to the large coupling constant between the α-proton and the pro-*R* β-hydrogen. In this conformation, any steric interactions affecting the hydrogen atom transfer would be expected to result in stereoselective loss of the pro-*S* hydrogen, as this site is the less hindered to the approach of the bromine atom and loss of this hydrogen would relieve steric interactions between the phenyl and phthalimido groups. The stereoselectivity is consistent with neighboring group participation by the amido substituent. Considering the conformations **B** and **C** of **1b** which have the correct orientation to undergo



hydrogen atom transfer with direct interaction between the amide group and the developing electron deficient center, the conformer **B** would be preferred on steric grounds and stereoselective loss of the pro-*R* hydrogen from this conformer would be expected.

Several alternative explanations for the kinetic effects observed in the reactions of **1a**−**f** and **3a**−**f** were considered, but these are inconsistent with the stereoselectivity observed in the reactions of **4a** and **4b**. In principal, the phthalimido group of **1a**−**f** could be involved in neighboring group participation, but this would be expected to result in stereoselective loss of the pro-*S* hydrogen from **1b**. This would occur from the conformer **A**, whereas loss of the pro-*R* hydrogen would involve the conformer **C**. Not only is the conformer **C** of much higher ground-state energy, reaction *via* that conformer would also involve the development of additional steric interactions between the phenyl and amido substituents in the reaction transition state. Another possible interpretation of the results is that the amido substituent of **1b**, **1d**, and **1f** coordinates to the bromine atom involved in the hydrogen atom abstraction [Br∴NH(tBu)COR], thereby facilitating reaction. Similar three-electron-bonded species have been proposed as intermediates, for example, in the reaction of amino acids with hydroxyl radical [HO∴NH_2-$CHRCO_2^-$][11] and in the radical-induced oxidation of sulfides [RR′S∴OCOR′],[12] and sulfide coordination of the bromine atom [R_2S∴Br] has been demonstrated.[13] A third alternative is that the reactions of **1b**, **1d**, and **1f** proceed *via* the corresponding *N*-bromoamides and involve intramolecular 1,4-hydrogen transfer to the amidyl radicals. In these cases, stereoselective loss of the pro-*S* hydrogen from **1b** would be expected, however, as this would involve less steric interactions between the phenyl and phthalimido substituents. To confirm this expectation, the *N*-bromoamides of **4a** and **4b** were prepared by treatment with *tert*-butylhypobromite and photolyzed at reflux in CCl_4. The bromoamide derived from the (2*S*,3*S*)-deuteride **4a** gave a mixture of the diastereomers of **5**, with each diastereomer containing 28% deuterium, whereas the bromoamide of the diastereomer **4b** gave **5**, with 85% deuterium retention. These results correlate with a deuterium isotope effect of 1.5 for the intramolecular 1,4-hydrogen atom transfer[10,14] and a stereoselectivity of 3.8 for abstraction of the pro-*S* hydrogen. Clearly this stereochemical outcome is different to that observed in the reactions of **4a** and **4b** with NBS and precludes the involvement of amidyl radicals as intermediates in the reactions of **1b**, **1d**, and **1f** with NBS.

In conclusion, all of the above evidence indicates that the reactions of **1a**−**f** with NBS involve anchimeric assistance in hydrogen atom abstraction by the bromine atom, through neighboring group participation by an adjacent protected carboxyl group. It appears that this may be a more specific phenomenon than the examples of 1,3-participation in atom transfer reactions reported previously.[1−4] While 1,3-participation occurs in reactions involving either hydrogen or halogen atom abstraction, with correspondingly electron rich or deficient transition states, and is also reflected in the bridging of the product radicals as determined by EPR spectroscopic studies,[15] neighboring group effects observed in the present work are apparently limited to hydrogen transfer reactions and the stabilization of electron deficient reaction transition states.

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(9) Compounds **4a** and **4b** were prepared as previously described for the corresponding methyl esters,[16] each in approximately 98% diastereomeric excess and with approximately 99% D_1 incorporation.

(10) Based on the assumption that the isotope effects for loss of the pro-*R* and pro-*S* hydrogens are identical.

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Appendix 3

Zeitschrift für Kristallographie 211, 289–290

Crystal structure of (*S*)-3-hydroxy-N-*tert*-butyl-N$^{\alpha}$-phthaloylvalinamide, $C_{17}H_{22}N_2O_4$

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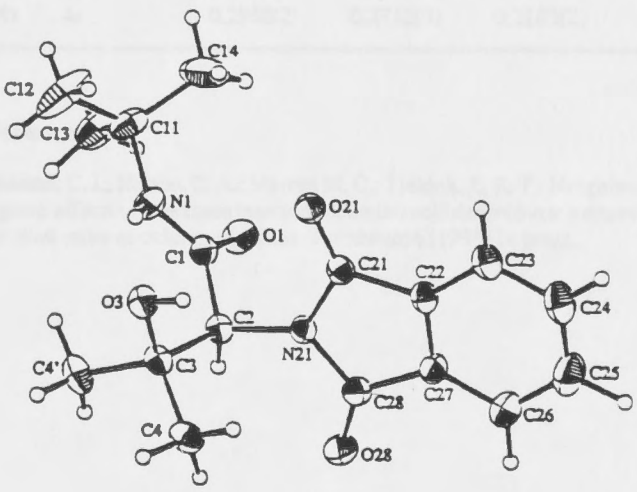


Source of material: see ref. 1; m. pt 408 K - 409 K.
The structure features both intra- and inter-molecular H bonding contacts. The N(1)H···O(3) separation is 2.04(1) Å and in the lattice O(3)H···O(1) is 1.88(3) Å such that O(1)···O(3) is 2.739(3) Å.

$C_{17}H_{22}N_2O_4$, monoclinic, $P12_1/c1$ (No. 14), a =11.242(4) Å, b =10.299(2) Å, c =14.908(3) Å, β =94.76(2)°, V =1720.1 Å^3, Z =4, $R(F)$ =0.038, $R_w(F)$ =0.036.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.24 x 0.40 x 0.56 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.88 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	50°
$N(hkl)_{unique}$:	4092
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	296
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1)	4*e*	0.685(2)	0.146(2)	0.318(2)	0.057(9)
H(2)	4*e*	0.465(2)	0.330(2)	0.329(1)	0.040(6)
H(3)	4*e*	0.510(3)	−0.012(3)	0.331(2)	0.13(1)
H(4'a)	4*e*	0.564(2)	0.156(3)	0.520(2)	0.084(9)
H(4'b)	4*e*	0.650(2)	0.228(3)	0.455(2)	0.080(9)
H(4'c)	4*e*	0.528(2)	0.302(3)	0.482(2)	0.076(9)
H(4a)	4*e*	0.324(2)	0.201(2)	0.419(2)	0.062(8)
H(4b)	4*e*	0.326(2)	0.077(2)	0.363(2)	0.061(8)
H(4c)	4*e*	0.374(2)	0.066(3)	0.464(2)	0.078(9)
H(12a)	4*e*	0.866(3)	0.058(4)	0.283(3)	0.15(2)
H(12b)	4*e*	0.968(3)	0.141(3)	0.293(2)	0.11(1)
H(12c)	4*e*	0.897(3)	0.135(4)	0.374(3)	0.15(2)
H(13a)	4*e*	0.863(3)	0.370(3)	0.359(2)	0.11(1)
H(13b)	4*e*	0.950(2)	0.367(3)	0.281(2)	0.078(9)
H(13c)	4*e*	0.821(3)	0.425(3)	0.265(2)	0.10(1)
H(14a)	4*e*	0.774(6)	0.279(8)	0.127(5)	0.36(1)
H(14b)	4*e*	0.888(3)	0.218(4)	0.137(2)	0.15(1)
H(14c)	4*e*	0.782(4)	0.145(5)	0.149(3)	0.19(2)
H(23)	4*e*	0.350(2)	0.007(2)	−0.004(2)	0.068(9)
H(24)	4*e*	0.161(2)	0.042(3)	−0.073(2)	0.08(1)
H(25)	4*e*	0.019(3)	0.185(3)	−0.021(2)	0.12(1)
H(26)	4*e*	0.076(2)	0.300(3)	0.119(2)	0.10(1)

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	4*e*	0.6120(2)	0.3846(2)	0.2259(1)	0.061(1)	0.065(1)	0.078(1)	0.004(1)	0.011(1)	0.030(1)
O(3)	4*e*	0.5541(2)	0.0381(2)	0.3677(1)	0.065(1)	0.039(1)	0.054(1)	0.0074(9)	−0.001(1)	0.0009(9)
O(21)	4*e*	0.5217(2)	0.0771(2)	0.1528(1)	0.060(1)	0.056(1)	0.054(1)	0.0143(9)	0.0027(9)	−0.004(1)
O(28)	4*e*	0.2572(2)	0.3488(2)	0.2676(1)	0.062(1)	0.079(1)	0.070(1)	0.021(1)	0.006(1)	−0.010(1)

Table 3. (Continued)

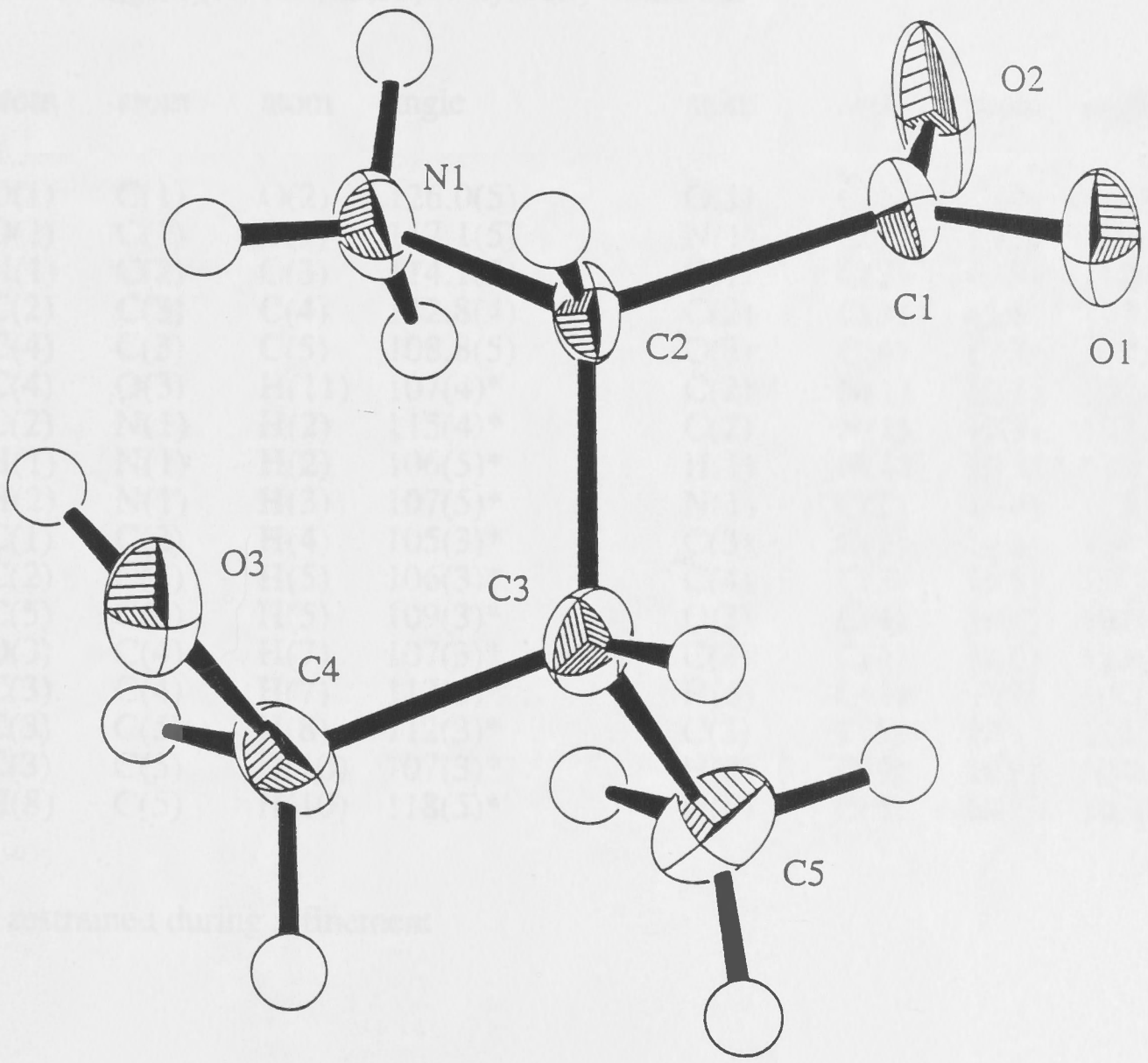
Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	4e	0.7026(2)	0.2153(2)	0.2939(2)	0.047(1)	0.046(2)	0.070(2)	0.002(1)	−0.001(1)	0.002(1)
N(21)	4e	0.4083(2)	0.2150(2)	0.2317(1)	0.046(1)	0.045(1)	0.041(1)	0.007(1)	−0.000(1)	−0.003(1)
C(1)	4e	0.6089(2)	0.2870(3)	0.2716(2)	0.052(2)	0.044(2)	0.045(2)	0.000(1)	−0.001(1)	0.002(1)
C(2)	4e	0.4921(2)	0.2491(2)	0.3074(2)	0.051(2)	0.036(2)	0.045(1)	0.003(1)	0.001(1)	−0.002(1)
C(3)	4e	0.4930(2)	0.1546(2)	0.3868(2)	0.060(2)	0.039(1)	0.041(1)	0.004(1)	0.002(1)	−0.001(1)
C(4)	4e	0.3685(3)	0.1238(3)	0.4093(2)	0.075(2)	0.049(2)	0.054(2)	0.002(2)	0.016(2)	0.002(2)
C(4')	4e	0.5614(3)	0.2150(4)	0.4679(2)	0.095(3)	0.056(2)	0.045(2)	−0.002(2)	−0.005(2)	−0.004(2)
C(11)	4e	0.8206(2)	0.2339(3)	0.2627(2)	0.040(2)	0.063(2)	0.101(3)	−0.003(2)	0.004(2)	−0.018(1)
C(12)	4e	0.8968(4)	0.1292(5)	0.3068(5)	0.049(2)	0.073(3)	0.262(8)	0.011(4)	−0.011(3)	−0.013(2)
C(13)	4e	0.8695(3)	0.3636(4)	0.2924(3)	0.057(2)	0.066(3)	0.126(4)	−0.008(2)	−0.003(2)	−0.005(2)
C(14)	4e	0.8110(4)	0.2238(7)	0.1604(3)	0.075(3)	0.226(7)	0.113(4)	−0.031(4)	0.041(3)	−0.080(4)
C(21)	4e	0.4298(2)	0.1320(2)	0.1618(2)	0.053(2)	0.042(2)	0.042(2)	0.000(1)	0.004(1)	0.005(1)
C(22)	4e	0.3193(2)	0.1315(2)	0.1011(2)	0.055(2)	0.047(2)	0.044(2)	−0.008(1)	−0.001(1)	0.006(1)
C(23)	4e	0.2913(3)	0.0659(3)	0.0224(2)	0.074(2)	0.056(2)	0.053(2)	−0.009(2)	−0.004(2)	0.000(2)
C(24)	4e	0.1798(3)	0.0882(4)	−0.0199(2)	0.090(3)	0.080(3)	0.061(2)	−0.020(2)	−0.016(2)	−0.005(2)
C(25)	4e	0.1020(3)	0.1721(4)	0.0139(3)	0.065(2)	0.103(3)	0.088(3)	−0.011(2)	−0.020(2)	0.002(2)
C(26)	4e	0.1311(3)	0.2386(4)	0.0926(2)	0.052(2)	0.094(3)	0.073(2)	−0.002(2)	−0.006(2)	−0.003(2)
C(27)	4e	0.2416(2)	0.2162(3)	0.1349(2)	0.043(2)	0.063(2)	0.051(2)	−0.003(1)	−0.000(1)	0.004(1)
C(28)	4e	0.2968(2)	0.2712(3)	0.2185(2)	0.049(2)	0.056(2)	0.050(2)	0.005(1)	0.007(1)	0.001(1)

Reference

1. Easton, C. J.; Hutton, C. A.; Merrett M. C.; Tiekink, E. R. T.: Neighbouring group effects in side chain reactions of amino acid derivatives: a stereocontrolled route to chloramphenicol. Tetrahedron (1996) in press.

Appendix 4

Crystal structure of (2*S*,3*S*)-4-hydroxyvaline **3a**.



Bond Lengths (Å) for (2*S*,3*S*)-4-hydroxyvaline **3a**.

atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.242(7)	O(2)	C(1)	1.252(7)
O(3)	C(4)	1.427(7)	N(1)	C(2)	1.473(8)
C(1)	C(2)	1.558(8)	C(2)	C(3)	1.523(7)
C(3)	C(4)	1.527(8)	C(3)	C(5)	1.523(8)
O(3)	H(11)	0.78(4)*	N(1)	H(1)	0.89(3)*
N(1)	H(2)	0.86(3)*	N(1)	H(3)	0.85(3)*
C(2)	H(4)	0.89(3)*	C(3)	H(5)	0.91(3)*
C(4)	H(6)	0.96(3)*	C(4)	H(7)	1.00(3)*
C(5)	H(8)	0.92(3)*	C(5)	H(9)	0.91(4)*
C(5)	H(10)	0.97(3)*			

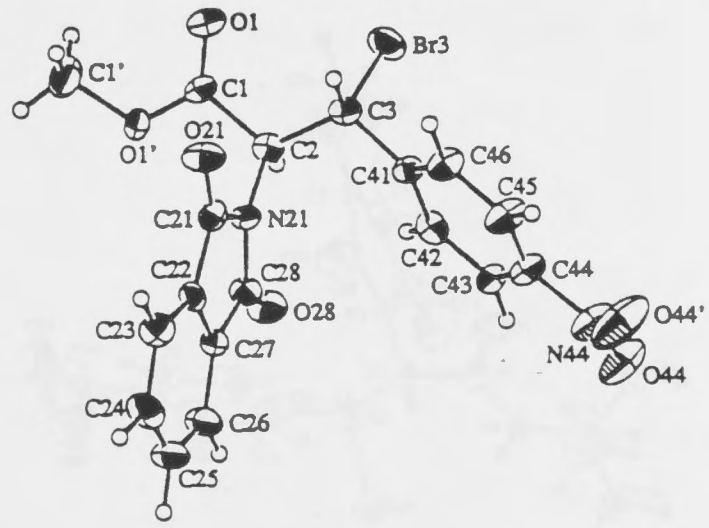
Bond Angles (Å) for (2*S*,3*S*)-4-hydroxyvaline **3a**.

atom	atom	atom	angle	atom	atom	atom	angle
O(1)	C(1)	O(2)	126.0(5)	O(1)	C(1)	C(2)	116.9(5)
O(2)	C(1)	C(2)	117.1(5)	N(1)	C(2)	C(1)	109.2(4)
N(1)	C(2)	C(3)	114.1(5)	C(1)	C(2)	C(3)	110.4(4)
C(2)	C(3)	C(4)	112.8(4)	C(2)	C(3)	C(5)	113.2(5)
C(4)	C(3)	C(5)	108.8(5)	O(3)	C(4)	C(3)	113.4(5)
C(4)	O(3)	H(11)	107(4)*	C(2)	N(1)	H(1)	103(4)*
C(2)	N(1)	H(2)	115(4)*	C(2)	N(1)	H(3)	107(4)*
H(1)	N(1)	H(2)	106(5)*	H(1)	N(1)	H(3)	119(5)*
H(2)	N(1)	H(3)	107(5)*	N(1)	C(2)	H(4)	113(3)*
C(1)	C(2)	H(4)	105(3)*	C(3)	C(2)	H(4)	104(3)*
C(2)	C(3)	H(5)	106(3)*	C(4)	C(3)	H(5)	107(3)*
C(5)	C(3)	H(5)	109(3)*	O(3)	C(4)	H(6)	101(3)*
O(3)	C(4)	H(7)	107(3)*	C(3)	C(4)	H(6)	113(3)*
C(3)	C(4)	H(7)	113(3)*	H(6)	C(4)	H(7)	109(4)*
C(3)	C(5)	H(8)	112(3)*	C(3)	C(5)	H(9)	112(4)*
C(3)	C(5)	H(10)	107(3)*	H(8)	C(5)	H(9)	104(5)*
H(8)	C(5)	H(10)	118(5)*	H(9)	C(5)	H(10)	105(4)*

* restrained during refinement

Appendix 5

Crystal structure of (2*S*,3*R*)-3-bromo-*N*-phthaloyl-*p*-nitrophenylalanine methyl ester **71a.**



The structure is shown to be *S* at both C(2) and C(3). The dihedral angle between the C(41)–C(46) and phthaloyl groups is 111.7° and a small twist about the C(44)–N(44) bond is noted; C(43)/C(44)/N(44)/ O(44) is 13(1)°.

$C_{18}H_{13}BrN_2O_6$, orthorhombic, $P2_12_12_1$ (No. 19), a =11.299(2) Å, b =19.642(1) Å, c =8.066(2) Å, V =1790.1 Å^3, Z =4, $R(F)$ =0.030, $R_w(F)$ =0.029.

Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.19 x 0.23 x 0.26 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	23.41 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	$\omega/2\theta$
$T_{measurement}$:	293 K
$2\theta_{max}$:	55°
$N(hkl)_{unique}$:	2468
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	245
Program:	teXsan

Final atomic coordinates and displacement parameters (in Å^2)

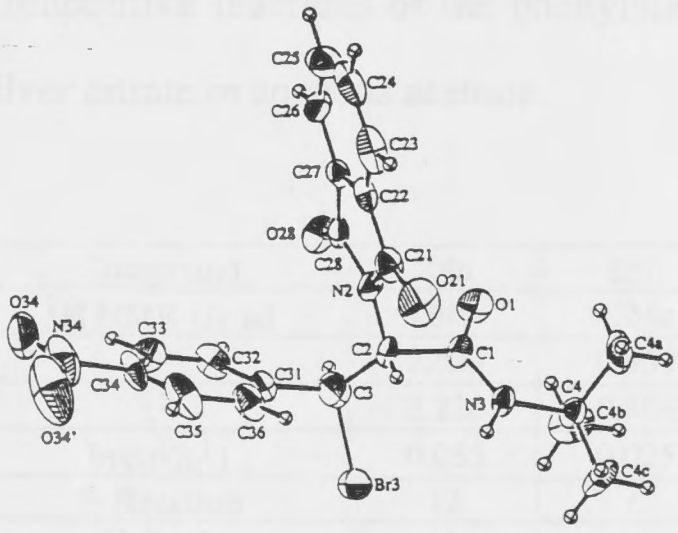
Atom	Site	x	y	z	U_{iso}
H(1'a)	4*a*	0.10208	0.25245	0.0689	0.08696
H(1'b)	4*a*	0.20696	0.21671	–0.02805	0.16837
H(1'c)	4*a*	0.09753	0.17315	0.03372	0.09145
H(2)	4*a*	0.27721	0.13305	0.46611	0.01322
H(3)	4*a*	0.47968	0.08675	0.30149	0.06300
H(23)	4*a*	0.58467	0.37157	0.27821	0.08217
H(24)	4*a*	0.57967	0.46313	0.46874	0.03593
H(25)	4*a*	0.48323	0.45286	0.71846	0.06891
H(26)	4*a*	0.37144	0.35659	0.78193	0.10184
H(42)	4*a*	0.37989	0.09896	0.72279	0.04710
H(43)	4*a*	0.50403	0.10364	0.95324	0.10901
H(45)	4*a*	0.78692	0.08401	0.65124	0.05231
H(46)	4*a*	0.66205	0.08193	0.41865	0.06136

Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(3)	4*a*	0.34492(6)	0.00098(5)	0.4113(1)	0.0695(5)	0.0393(3)	0.0836(6)	–0.0057(8)	–0.0057(6)	–0.0085(7)
O(1)	4*a*	0.3071(4)	0.1116(3)	0.1062(6)	0.064(4)	0.066(3)	0.044(3)	–0.009(3)	–0.000(3)	–0.015(3)
O(1')	4*a*	0.2093(5)	0.1984(3)	0.2157(7)	0.068(4)	0.053(4)	0.040(4)	0.018(3)	–0.011(3)	0.004(3)
O(21)	4*a*	0.4965(5)	0.2285(3)	0.2041(7)	0.078(4)	0.064(3)	0.042(4)	–0.022(3)	0.028(4)	–0.011(3)
O(28)	4*a*	0.2867(5)	0.2226(3)	0.6760(7)	0.081(5)	0.066(4)	0.040(3)	–0.011(3)	0.025(4)	–0.000(3)
O(44)	4*a*	0.6871(6)	0.0824(4)	1.0952(8)	0.101(6)	0.164(7)	0.046(4)	–0.003(5)	–0.012(5)	0.002(5)
O(44')	4*a*	0.8352(6)	0.0930(4)	0.9392(9)	0.065(4)	0.26(1)	0.072(5)	–0.011(7)	–0.016(6)	–0.010(6)
N(21)	4*a*	0.3877(5)	0.2086(3)	0.4349(7)	0.048(4)	0.034(3)	0.029(4)	–0.008(4)	0.003(3)	–0.003(3)
N(44)	4*a*	0.7303(8)	0.0896(4)	0.960(1)	0.077(6)	0.118(7)	0.051(6)	–0.015(5)	–0.014(6)	–0.009(6)
C(1)	4*a*	0.2843(7)	0.1484(4)	0.2180(9)	0.048(5)	0.049(5)	0.033(5)	–0.012(4)	–0.003(4)	–0.004(4)
C(1')	4*a*	0.1489(8)	0.2113(4)	0.060(1)	0.084(7)	0.091(7)	0.055(6)	0.011(6)	–0.011(7)	0.015(6)
C(2)	4*a*	0.3401(6)	0.1436(3)	0.3884(9)	0.037(4)	0.042(4)	0.040(5)	–0.005(4)	0.009(5)	–0.001(4)
C(3)	4*a*	0.4310(6)	0.0865(3)	0.401(1)	0.045(5)	0.043(4)	0.042(5)	–0.009(4)	0.005(5)	–0.003(4)
C(21)	4*a*	0.4604(7)	0.2468(4)	0.335(1)	0.035(5)	0.052(5)	0.039(5)	–0.001(5)	–0.001(4)	0.004(4)
C(22)	4*a*	0.4778(6)	0.3109(3)	0.423(1)	0.036(4)	0.034(4)	0.056(5)	0.005(5)	–0.009(5)	–0.002(3)
C(23)	4*a*	0.5408(7)	0.3683(4)	0.381(1)	0.052(5)	0.056(5)	0.059(6)	–0.013(5)	–0.003(5)	0.001(4)
C(24)	4*a*	0.5384(8)	0.4211(4)	0.494(1)	0.062(6)	0.036(5)	0.098(8)	–0.016(5)	–0.012(6)	–0.007(5)
C(25)	4*a*	0.4795(9)	0.4156(5)	0.640(1)	0.079(8)	0.058(6)	0.068(8)	0.004(6)	–0.014(7)	–0.026(6)
C(26)	4*a*	0.4156(7)	0.3595(4)	0.679(1)	0.073(6)	0.049(5)	0.057(6)	–0.001(5)	0.002(5)	–0.016(5)
C(27)	4*a*	0.4162(6)	0.3081(3)	0.569(1)	0.047(5)	0.039(4)	0.037(5)	0.004(4)	0.001(5)	–0.004(4)
C(28)	4*a*	0.3528(8)	0.2432(4)	0.576(1)	0.059(5)	0.048(4)	0.031(5)	0.004(4)	0.017(6)	–0.002(5)
C(41)	4*a*	0.5090(6)	0.0906(3)	0.5486(9)	0.043(5)	0.041(4)	0.033(5)	–0.007(4)	0.004(4)	–0.001(4)
C(42)	4*a*	0.4649(7)	0.0962(4)	0.707(1)	0.039(5)	0.043(5)	0.055(6)	–0.002(4)	0.016(5)	0.008(4)
C(43)	4*a*	0.5360(8)	0.0979(4)	0.843(1)	0.064(7)	0.051(6)	0.038(6)	0.002(5)	–0.009(5)	0.000(5)
C(44)	4*a*	0.6544(8)	0.0913(4)	0.816(1)	0.055(5)	0.065(5)	0.037(5)	–0.016(4)	–0.005(6)	0.001(6)
C(45)	4*a*	0.7018(7)	0.0867(5)	0.665(1)	0.037(5)	0.108(7)	0.045(6)	–0.005(6)	0.006(5)	–0.010(5)
C(46)	4*a*	0.6286(7)	0.0859(4)	0.529(1)	0.043(6)	0.071(6)	0.039(6)	–0.009(5)	0.007(5)	–0.000(5)

Appendix 6

Crystal structure of (2*RS*,3*SR*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide



The dihedral angle between the C(31)–C(36) and phthaloyl groups is 110.6°. Hydrogen bonding the lattice occurs between the N(3)–H and O(28) atoms such that H(3)···O(28) is 2.21 Å and N(3)···O(28) is 3.16(1) Å.

$C_{21}H_{20}BrN_3O_5$, monoclinic, $P12_1/n1$ (No. 14), a =10.900(5) Å, b =11.189(6) Å, c =18.285(4) Å, β =103.10(2)°, V =2172.8 Å^3, Z =4, $R(F)$ =0.047, $R_w(F)$ =0.037.

Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.07 x 0.16 x 0.36 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	19.35 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	50°
N(hkl)$_{unique}$:	4058
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
N($param$)$_{refined}$:	271
Program:	teXsan

Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(2)	4*e*	–0.27611	–0.14957	–0.75497	0.10104
H(3')	4*e*	–0.46030	–0.18462	–0.75327	0.09207
H(3)	4*e*	–0.26753	0.05770	–0.81770	0.09406
H(4c)	4*e*	–0.50644	–0.03443	–0.59803	0.09801
H(4d)	4*e*	–0.60326	0.08314	–0.71652	0.10167
H(4e)	4*e*	–0.73425	0.02275	–0.71540	0.10167
H(4f)	4*e*	–0.67814	0.01249	–0.78784	0.10167
H(4g)	4*e*	–0.68504	–0.21079	–0.78710	0.09288
H(4h)	4*e*	–0.74916	–0.20537	–0.71762	0.09288
H(4i)	4*e*	–0.62516	–0.28172	–0.71259	0.12685
H(4a)	4*e*	–0.52359	–0.17503	–0.59839	0.09801
H(4b)	4*e*	–0.64110	–0.09037	–0.60142	0.09801
H(23)	4*e*	0.09440	–0.24695	–0.53057	0.09207
H(24)	4*e*	0.25165	–0.12344	–0.45802	0.09095
H(25)	4*e*	0.27409	0.07115	–0.48074	0.10727
H(26)	4*e*	0.13103	0.16555	–0.57853	0.0784
H(32)	4*e*	–0.12542	0.12761	–0.87005	0.07925
H(33)	4*e*	0.05122	0.10325	–0.91680	0.0889
H(35)	4*e*	0.03505	–0.25429	–0.89274	0.09105
H(36)	4*e*	–0.14418	–0.23138	–0.84222	0.09429

Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(3)	4*e*	–0.4198(1)	–0.0577(1)	–0.89881(6)	0.0740(8)	0.0761(8)	0.0662(7)	–0.007(1)	0.0102(5)	–0.004(1)
O(1)	4*e*	–0.3736(7)	0.0567(7)	–0.6764(4)	0.093(6)	0.046(5)	0.104(6)	–0.014(5)	0.033(5)	–0.029(5)
O(21)	4*e*	–0.1494(9)	–0.2462(8)	–0.6522(5)	0.19(1)	0.049(5)	0.152(8)	–0.045(6)	0.072(7)	0.004(6)
O(28)	4*e*	–0.0976(7)	0.1436(6)	–0.7058(4)	0.078(6)	0.041(6)	0.101(7)	–0.003(5)	0.027(5)	0.013(5)
O(34)	4*e*	0.226(1)	–0.000(2)	–0.9453(8)	0.11(1)	0.37(3)	0.086(9)	–0.05(1)	0.042(7)	0.03(1)
N(2)	4*e*	–0.1507(7)	–0.054(1)	–0.6949(4)	0.052(6)	0.057(6)	0.059(6)	–0.021(7)	0.017(5)	0.013(7)
N(3)	4*e*	–0.4719(8)	–0.1123(7)	–0.7264(4)	0.047(6)	0.038(6)	0.070(6)	–0.006(5)	0.032(5)	–0.012(5)
N(34)	4*e*	0.177(2)	–0.091(2)	–0.933(1)	0.13(2)	0.19(3)	0.08(1)	0.05(1)	0.05(1)	0.06(2)
C(1)	4*e*	–0.378(1)	–0.032(1)	–0.7144(6)	0.057(9)	0.05(1)	0.072(9)	–0.009(7)	0.027(7)	0.011(8)
C(2)	4*e*	–0.267(1)	–0.064(1)	–0.7494(7)	0.051(8)	0.14(1)	0.062(8)	–0.04(1)	0.029(7)	–0.002(9)
C(3)	4*e*	–0.267(1)	–0.029(1)	–0.8219(7)	0.068(9)	0.15(1)	0.070(9)	0.00(1)	0.016(8)	–0.004(9)
C(4)	4*e*	–0.589(1)	–0.1001(9)	–0.7025(6)	0.043(8)	0.057(9)	0.073(9)	–0.000(7)	0.022(7)	–0.006(6)
C(4a)	4*e*	–0.563(1)	–0.100(1)	–0.6174(7)	0.083(9)	0.13(1)	0.10(1)	0.003(9)	0.059(8)	–0.001(8)
C(4b)	4*e*	–0.6575(9)	0.015(1)	–0.7334(6)	0.075(9)	0.07(1)	0.14(1)	0.036(8)	0.006(8)	–0.023(8)
C(4c)	4*e*	–0.6695(9)	–0.210(1)	–0.7327(6)	0.048(7)	0.08(1)	0.14(1)	–0.024(8)	0.022(7)	–0.016(7)
C(21)	4*e*	–0.100(1)	–0.149(1)	–0.6478(7)	0.09(1)	0.05(1)	0.066(9)	–0.012(9)	0.037(8)	0.007(9)
C(22)	4*e*	0.013(1)	–0.102(1)	–0.5989(7)	0.06(1)	0.07(1)	0.055(9)	0.015(8)	0.035(7)	0.004(8)
C(23)	4*e*	0.099(2)	–0.162(1)	–0.541(1)	0.13(1)	0.08(1)	0.10(1)	0.02(1)	0.07(1)	0.02(1)
C(24)	4*e*	0.192(2)	–0.088(2)	–0.500(1)	0.10(2)	0.17(2)	0.07(1)	0.05(1)	0.04(1)	0.02(2)
C(25)	4*e*	0.206(2)	0.026(2)	–0.512(1)	0.06(1)	0.21(2)	0.08(1)	–0.00(2)	0.014(9)	–0.05(2)
C(26)	4*e*	0.123(1)	0.081(1)	–0.5688(7)	0.053(8)	0.10(1)	0.087(9)	–0.021(9)	0.033(7)	–0.029(9)
C(27)	4*e*	0.027(1)	0.015(1)	–0.6126(6)	0.067(9)	0.04(1)	0.048(8)	–0.010(7)	0.029(7)	–0.009(7)
C(28)	4*e*	–0.077(1)	0.048(1)	–0.6762(6)	0.053(7)	0.053(9)	0.057(8)	–0.006(9)	0.032(6)	0.00(1)
C(31)	4*e*	–0.154(1)	–0.049(2)	–0.8535(6)	0.065(9)	0.09(1)	0.045(7)	–0.00(1)	0.025(6)	–0.01(1)
C(32)	4*e*	–0.093(2)	0.048(1)	–0.8745(7)	0.09(1)	0.06(1)	0.072(9)	0.03(1)	0.020(8)	–0.01(1)
C(33)	4*e*	0.010(2)	0.034(1)	–0.9012(7)	0.08(1)	0.06(1)	0.09(1)	0.001(9)	0.020(8)	0.00(1)
C(34)	4*e*	0.058(1)	–0.075(2)	–0.9066(7)	0.06(1)	0.14(2)	0.048(7)	0.06(1)	0.027(7)	0.02(1)
C(35)	4*e*	0.002(2)	–0.175(1)	–0.8869(8)	0.15(2)	0.07(1)	0.08(1)	0.052(9)	0.05(1)	0.02(1)
C(36)	4*e*	–0.104(2)	–0.162(2)	–0.8586(7)	0.12(1)	0.06(1)	0.07(1)	0.001(8)	0.041(9)	–0.00(1)

Appendix 7

Competitive reactions of the phenylalanine derivatives **18a**, **18b**, **20a** and **20b** with silver nitrate in aqueous acetone.

Compound	**18a**	**18b**	**55 + 56**	**20a**	**20b**	**60**
^{1}H NMR signal	OMe	OMe	OMe	CMe_3	CMe_3	α-H
t^0	2.529	0.853		4.147	5.353	
t^1	2.226	0.806	0.387	1.452	2.081	5.952
$\log(t^0/t^1)$	0.055	0.025		0.456	0.410	
% Reaction	12	6		65	61	
% final	66	24	11	15	22	63
% accounted for		101			100	
k_{rel} (Ag^+/H_2O)	2.2	1.0		18.2	16.4	

Compound	**18a**	**18b**	**55 + 56**	**20a**	**20b**	**60**
^{1}H NMR signal	OMe	OMe	OMe	CMe_3	CMe_3	α-H
t^0	1.450	0.500		2.333	3.000	
t^1	1.215	0.467	0.359	0.720	0.963	3.785
$\log(t^0/t^1)$	0.077	0.030		0.510	0.493	
% Reaction	16	7		69	68	
% final	62	24	18	14	18	71
% accounted for		104			103	
k_{rel} (Ag^+/H_2O)	2.6	1.0		17.0	16.4	

Compound	**18a**	**18b**	**55 + 56**	**20a**	**20b**	**60**
^{1}H NMR signal	OMe	OMe	OMe	CMe_3	CMe_3	α-H
t^0	1.938	0.656		3.219	4.500	
t^1	1.600	0.588	0.495	1.125	1.463	5.625
$\log(t^0/t^1)$	0.083	0.048		0.457	0.488	
% Reaction	17	10		65	67	
% final	62	23	19	15	19	73
% accounted for		104			107	
k_{rel} (Ag^+/H_2O)	1.7	1.0		9.5	10.2	

Appendix 8

Competitive reactions of the valine derivatives **33** and **73** with silver nitrate in aqueous acetone.

Compound	**33**	**34**	**38 + 98**	**73**	**111**	**112**
^{1}H NMR signal	OMe	OMe	OMe	CMe_3	CMe_3	CMe_3
t^0	2.941			9.941		
t^1	2.486	0.029	0.083	4.000	3.429	1.714
$\log(t^0/t^1)$	0.073			0.395		
% Reaction	15			60		
% final	85	1	3	40	34	17
% accounted for	89			92		
k_{rel} (Ag^+/H_2O)	1.0			5.4		

Compound	**33**	**34**	**38 + 98**	**73**	**111**	**112**
^{1}H NMR signal	OMe	OMe	OMe	CMe_3	CMe_3	CMe_3
t^0	2.087			7.348		
t^1	1.796	0.047	0.070	2.889	2.556	1.278
$\log(t^0/t^1)$	0.065			0.405		
% Reaction	14			61		
% final	86	2	3	39	35	17
% accounted for	91			91		
k_{rel} (Ag^+/H_2O)	1.0			6.2		

Appendix 9

Competitive reaction of the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** with silver sulfate in aqueous acetone.

Compound	**71b**	**71a**	**114**	**72b**	**72a**	**117**
^{1}H NMR signal	OMe	OMe	OMe	CMe_3	CMe_3	α-H
t^0	0.554	0.649		1.987	2.216	
t^1	0.230	0.027	0.014	0.689	0.635	1.635
$\log(t^0/t^1)$	0.382	1.381		0.460	0.543	
% Reaction	58	96		65	71	
% final	19	2	1	16	15	39
% accounted for	22			70		
k_{rel} (Ag^+/H_2O)	1.0	3.6		1.2	1.4	

Compound	**71b**	**71a**	**114**	**72b**	**72a**	**117**
^{1}H NMR signal	OMe	OMe	OMe	CMe_3	CMe_3	α-H
t^0	0.694	0.861		2.222	2.514	
t^1	0.400	0.046	0.015	1.446	1.554	1.138
$\log(t^0/t^1)$	0.240	1.270		0.187	0.209	
% Reaction	42	95		34	38	
% final	26	3	1	31	33	24
% accounted for	30			88		
k_{rel} (Ag^+/H_2O)	1.3	6.8		1.0	1.1	

Appendix 10

Competitive reactions of the phenylalanine derivatives **20a** and **20b** with silver nitrate in deuterium oxide and acetone.

Compound	**20a**	**20b**	**60**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	1.588	2.000	
t^1	0.784	1.081	1.973
$\log(t^0/t^1)$	0.307	0.267	
% Reaction	51	46	
% final	22	30	55
% accounted for		107	
k_{rel} (Ag^+/H_2O)	1.1	1.0	

Compound	**20a**	**20b**	**60**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	1.957	2.486	
t^1	1.313	1.792	1.583
$\log(t^0/t^1)$	0.173	0.142	
% Reaction	33	28	
% final	30	40	36
% accounted for		106	
k_{rel} (Ag^+/H_2O)	1.2	1.0	

Compound	**20a**	**20b**	**60**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	1.106	1.416	
t^1	0.360	0.500	1.740
$\log(t^0/t^1)$	0.487	0.452	
% Reaction	67	65	
% final	14	20	69
% accounted for		103	
k_{rel} (Ag^+/H_2O)	1.1	1.0	

Compound	**20a**	**20b**	**60**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	1.106	1.416	
t^1	0.411	0.597	1.705
$\log(t^0/t^1)$	0.430	0.388	
% Reaction	63	59	
% final	16	24	68
% accounted for		108	
k_{rel} (Ag^+/H_2O)	1.1	1.0	

Appendix 11

Competitive reactions of the phenylalanine derivatives **17** and **19** with NBS.

compound	**19**	**20a + 20b**	**17**	**18a + 18b**
^{1}H NMR signal	CMe_3	CMe_3	OMe	OMe
t^0	1.694		0.495	
t^1	0.381	0.885	0.363	0.071
$\log(t^0/t^1)$	0.648		0.135	
% reaction	78		27	
% final	22	52	73	14
% accounted for	75		88	
k_{rel} (NBS)	4.8		1	

compound	**19**	**20a + 20b**	**17**	**18a + 18b**
^{1}H NMR signal	CMe_3	CMe_3	OMe	OMe
t^0	2.657		0.800	
t^1	1.360	1.180	0.700	0.160
$\log(t^0/t^1)$	0.291		0.058	
% reaction	49		12	
% final	51	44	88	20
% accounted for	96		108	
k_{rel} (NBS)	5.0		1	

compound	**19**	**20a + 20b**	**17**	**18a + 18b**
^{1}H NMR signal	CMe_3	CMe_3	OMe	OMe
t^0	1.802		0.495	
t^1	0.825	0.794	0.421	0.063
$\log(t^0/t^1)$	0.339		0.070	
% reaction	54		15	
% final	46	44	85	13
% accounted for	90		98	
k_{rel} (NBS)	4.8		1	

Competitive reactions of the tyrosine derivatives **79a** and **79b** with NBS.

compound	**79a**	**80a + 80b**	**79b**	**81a + 81b**
^{1}H NMR signal	OMe	OMe	CMe_3	CMe_3
t^0	0.905		2.337	
t^1	0.600	0.173	0.600	1.433
$\log(t^0/t^1)$	0.179		0.591	
% reaction	34		74	
% final	66	19	26	61
% accounted for	85		87	
k_{rel} (NBS)	1		3.3	

compound	**79a**	**80a + 80b**	**79b**	**81a + 81b**
^{1}H NMR signal	OMe	OMe	CMe_3	CMe_3
t^0	1.351		3.649	
t^1	0.954	0.296	0.981	2.389
$\log(t^0/t^1)$	0.151		0.571	
% reaction	29		73	
% final	71	22	27	65
% accounted for	93		92	
k_{rel} (NBS)	1		3.8	

Competitive reactions of the nitrophenylalanine derivatives **78a** and **78b** with NBS.

compound	**78a**	**71a + 71b**	**78b**	**72a + 72b**
^{1}H NMR signal	OMe	OMe	CMe3	CMe3
t^0	0.569		1.466	
t^1	0.410	0.128	0.231	0.974
$\log(t^0/t^1)$	0.142		0.803	
% reaction	28		84	
% final	72	22	16	66
% accounted for	95		82	
k_{rel} (NBS)	1		5.6	

compound	**78a**	**71a + 71b**	**78b**	**72a + 72b**
^{1}H NMR signal	OMe	OMe	CMe_3	CMe_3
t^0	0.339		0.957	
t^1	0.222	0.065	0.119	0.670
$\log(t^0/t^1)$	0.184		0.905	
% reaction	35		88	
% final	65	19	12	70
% accounted for	85		82	
k_{rel} (NBS)	1		4.9	

Competitive reactions of the phenylalanine derivatives **17** and the nitrophenylalanine derivative **78b** with NBS.

compound	**17**	**18a + 18b**	**78b**	**72a + 72b**
^{1}H NMR signal	OMe	OMe	CMe_3	CMe_3
t^0	0.361		0.889	
t^1	0.125	0.229	0.469	0.313
$\log(t^0/t^1)$	0.461		0.278	
% reaction	64		48	
% final	36	63	52	35
% accounted for	99		87	
k_{rel} (NBS)	1.7		1	

compound	**17**	**18a + 18b**	**78b**	**72a + 72b**
^{1}H NMR signal	OMe	OMe	CMe_3	CMe_3
t^0	0.393		0.617	
t^1	0.189	0.171	0.394	0.171
$\log(t^0/t^1)$	0.318		0.195	
% reaction	52		36	
% final	48	44	64	28
% accounted for	92		92	
k_{rel} (NBS)	1.6		1	

Competitive reactions of the tyrosine derivative **79a** and the phenylalanine derivative **19** with NBS.

compound	**79a**	**80a + 80b**	**19**	**20a + 20b**
^{1}H NMR signal	OMe	OMe	CMe_3	CMe_3
t^0	1.378		2.844	
t^1	1.120	0.240	1.070	1.810
$\log(t^0/t^1)$	0.090		0.425	
% reaction	19		62	
% final	81	17	38	64
% accounted for	98		102	
k_{rel} (NBS)	1		4.7	

compound	**79a**	**80a + 80b**	**19**	**20a + 20b**
^{1}H NMR signal	OMe	OMe	CMe_3	CMe_3
t^0	0.603		1.863	
t^1	0.467	0.121	0.577	1.165
$\log(t^0/t^1)$	0.111		0.509	
% reaction	23		69	
% final	77	20	31	63
% accounted for	97		94	
k_{rel} (NBS)	1		4.6	

Appendix 12

Competitive reactions of the nitrophenylalanine derivatives **71a**, **71b**, **72a** and **72b** with triphenyltin hydride.

Compound	**71b**	**71a**	**78a**	**72b**	**78b**
^{1}H NMR signal	OMe	OMe	OMe	CMe3	CMe3
t^0	3.389	2.667		5.611	
t^1	2.346	1.192	1.795	3.308	1.577
$\log(t^0/t^1)$	0.160	0.350		0.229	
% Reaction	31	55		41	
% in final mixture	38	20	30	59	28
% Accounted for		88		87	
k_{rel}	1.0	2.2	1.1*	1.4	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Compound	**71b**	**71a**	**78a**	**72b**	**72a**	**78b**
^{1}H NMR signal	OMe	OMe	OMe	CMe3	CMe3	CMe3
t^0	1.163	0.857		2.061	1.184	
t^1	0.547	0.253	0.886	0.893	0.373	1.360
$\log(t^0/t^1)$	0.328	0.530		0.363	0.502	
% Reaction	53	70		57	68	
% in final mixture	27	13	44	28	11	42
% Accounted for		84			81	
k_{rel}	1.0	1.6	1.0*	1.1	1.5	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Competitive reactions of the tyrosine derivatives **81a** and **81b** and the phenylalanine derivatives **18a** and **18b** with triphenyltin hydride.

Compound	**81a**	**81b**	**79b**	**18a**	**18b**	**17**
^{1}H NMR signal	β-	β-	α-	β-	α-	α-
t^0	0.250	0.329		0.250	0.487	
t^1	0.104	0.166	0.311	0.104	0.290	0.321
$\log(t^0/t^1)$	0.381	0.297		0.381	0.225	
% Reaction	58	50		58	40	
% in final mixture	18	29	54	14	39	44
% Accounted for		101			97	
k_{rel}	1.7	1.3	1.2*	1.7	1.0	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Compound	**81a**	**81b**	**79b**	**18a**	**18b**	**17**
^{1}H NMR signal	β-	β-	α-	β-	α-	α-
t^0	0.390	0.520		0.390	0.780	
t^1	0.144	0.255	0.497	0.183	0.444	0.458
$\log(t^0/t^1)$	0.433	0.309		0.329	0.245	
% Reaction	63	51		53	43	
% in final mixture	16	28	55	16	38	39
% Accounted for		99			93	
k_{rel}	1.8	1.3	1.4*	1.3	1.0	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Competitive reactions of the tyrosine derivatives **80a** and **80b** and the nitrophenylalanine derivatives **72a** and **72b** with triphenyltin hydride.

Compound	**80a**	**80b**	**79a**	**72b**	**72a**	**78b**
^{1}H NMR signal	α-	α-	α-	α-	α-	α-
t^0	0.335	0.299		0.168	0.323	
t^1	0.217	0.223	0.072	0.030	0.042	0.163
$\log(t^0/t^1)$	0.189	0.128		0.746	0.884	
% Reaction	35	25		82	87	
% in final mixture	34	35	11	6	9	33
% Accounted for		80			48	
k_{rel}	1.5	1.0	1.0*	5.8	6.9	2.9*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Compound	**80a**	**80b**	**79a**	**72b**	**72a**	**78b**
^{1}H NMR signal	α-	α-	α-	α-	α-	α-
t^0	0.596	0.539		0.289	0.577	
t^1	0.364	0.349	0.126	0.035	0.063	0.294
$\log(t^0/t^1)$	0.215	0.188		0.916	0.962	
% Reaction	39	35		88	89	
% in final mixture	32	31	11	4	7	34
% Accounted for		74			45	
k_{rel}	1.1	1.0	1.0*	4.9	5.1	3.1*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Competitive reactions of the tyrosine derivatives **80a**, **80b**, **81a** and **81b** with triphenyltin hydride.

Compound	**80b**	**80a**	**79a**	**81b**	**81a**	**79b**
^{1}H NMR signal	α-	α-	α-	β-	β-	α-
t^0	0.259	0.281		0.273	0.245	
t^1	0.119	0.076	0.238	0.103	0.086	0.238*
$\log(t^0/t^1)$	0.338	0.568		0.423	0.455	
% Reaction	54	73		62	65	
% in final mixture	22	14	44	20	17	46
% Accounted for		80			83	
k_{rel}	1.0	1.7	1.0*	1.3	1.3	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Compound	**80a**	**80b**	**79a**	**81b**	**81a**	**79b**
^{1}H NMR signal	α-	α-	α-	β-	β-	α-
t^0	0.797	0.824		0.703	0.608	
t^1	0.235	0.364	0.494*	0.272	0.198	0.469*
$\log(t^0/t^1)$	0.530	0.355		0.412	0.487	
% Reaction	71	56		61	67	
% in final mixture	14	22	30	21	15	36
% Accounted for		66			72	
k_{rel}	1.5	1.0	1.0*	1.2	1.4	1.2*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Competitive reactions of the phenylalanine derivatives **18a**, **20a** and **20b** and with triphenyltin hydride.

Compound	**20a**	**20b**	**19**	**18a**	**17**
^{1}H NMR signal	α-	α-	α-	β-	α-
t^0	0.323	0.410		0.268	
t^1	0.090	0.138	0.317	0.083	0.110
$\log(t^0/t^1)$	0.555	0.473		0.509	
% Reaction	72	66		69	
% in final mixture	12	19	43	31	41
% Accounted for		74		72	
k_{rel}	1.2	1.0	1.1*	1.1	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Compound	**20a**	**20b**	**19**	**18a**	**17**
^{1}H NMR signal	α-	α-	α-	β-	α-
t^0	0.929	1.295		0.473	
t^1	0.629	0.776	0.882	0.310	0.176
$\log(t^0/t^1)$	0.169	0.222		0.183	
% Reaction	32	40		34	
% in final mixture	28	35	40	66	37
% Accounted for		103		103	
k_{rel}	1.0	1.3	1.1*	1.1	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Competitive reactions of the nitrophenylalanine derivatives **71a** and **71b** and the phenylalanine derivatives **20a** and **20b** with triphenyltin hydride.

Compound	**71b**	**71a**	**78a**	**20a**	**20b**	**19**
^{1}H NMR signal	OMe	OMe	OMe	CMe3	CMe3	CMe3
t^0	1.696	1.674		2.044	2.652	
t^1	0.662	0.338	0.506	1.688	2.117	0.519*
$\log(t^0/t^1)$	0.409	0.695		0.083	0.098	
% Reaction	61	80		17	20	
% in final mixture	20	10	15	36	45	11
% Accounted for		45			92	
k_{rel}	4.9	8.4	1.4*	1.0	1.2	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Compound	**71b**	**71a**	**78a**	**20a**	**20b**	**19**
^{1}H NMR signal	OMe	OMe	OMe	CMe3	CMe3	CMe3
t^0	1.236	1.273		1.709	2.273	
t^1	0.449	0.192	0.513	1.487	1.897	0.321*
$\log(t^0/t^1)$	0.440	0.822		0.060	0.079	
% Reaction	64	85		13	17	
% in final mixture	18	8	20	37	48	8
% Accounted for		46			93	
k_{rel}	7.3	13.7	2.5*	1.0	1.3	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Competitive reactions of the nitrophenylalanine derivatives **72a** and **72b** and the phenylalanine derivatives **18a** and **18b** with triphenyltin hydride.

Compound	**72b**	**72a**	**78b**	**18a**	**18b**	**17**
^{1}H NMR signal	CMe3	CMe3	CMe3	OMe	OMe	OMe
t^0	3.111	1.583		1.333	0.472	
t^1	0.310	0.119	1.071	1.000	0.405	0.095
$\log(t^0/t^1)$	1.002	1.124		0.125	0.066	
% Reaction	90	92		25	14	
% in final mixture	7	3	23	55	22	5
% Accounted for		33			83	
k_{rel}	15.2	17.0	4.3*	1.9	1.0	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Compound	**72b**	**72a**	**78b**	**18a**	**18b**	**17**
^{1}H NMR signal	CMe3	CMe3	CMe3	OMe	OMe	OMe
t^0	2.600	1.380		1.100	0.420	
t^1	0.242	0.091	0.682	0.788	0.349	0.030*
$\log(t^0/t^1)$	1.030	1.181		0.145	0.081	
% Reaction	91	93		28	17	
% in final mixture	6	2	17	52	23	2
% Accounted for		26			77	
k_{rel}	12.7	14.6	8.7*	1.8	1.0	1.0*

* denotes relative rate of formation based on product ratios, corrected to account for the ratio of the brominated substrates in the initial mixtures.

Competitive reactions of the phenylalanine derivatives **20a** and **20b** with triphenyltin hydride.

Compound	**20a**	**20b**	**19**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	0.852	1.120	
t^1	0.496	0.663	0.236
$\log(t^0/t^1)$	0.235	0.228	
% Reaction	42	41	
% in final mixture	58	59	12
% Accounted for		71	
k_{rel}	1.0	1.0	

Compound	**20a**	**20b**	**19**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	1.104	1.420	
t^1	0.363	0.468	1.105
$\log(t^0/t^1)$	0.446	0.482	
% Reaction	67	67	
% in final mixture	33	33	44
% Accounted for		77	
k_{rel}	1.0	1.0	

Compound	**20a**	**20b**	**19**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	1.179	1.573	
t^1	0.668	0.909	0.519
$\log(t^0/t^1)$	0.247	0.238	
% Reaction	43	42	
% in final mixture	57	58	19
% Accounted for		76	
k_{rel}	1.0	1.0	

Competitive reactions of the phenylalanine derivatives **18a** and **18b** with triphenyltin hydride.

Compound	**18a**	**18b**	**17**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	0.479	1.042	
t^1	0.177	0.463	0.415
$\log(t^0/t^1)$	0.432	0.352	
% Reaction	63	56	
% in final mixture	37	44	27
% Accounted for		69	
k_{rel}	1.2	1.0	

Compound	**18a**	**18b**	**17**
^{1}H NMR signal	CMe_3	CMe_3	CMe_3
t^0	0.651	1.410	
t^1	0.281	0.674	0.854
$\log(t^0/t^1)$	0.365	0.321	
% Reaction	57	52	
% in final mixture	43	48	41
% Accounted for		88	
k_{rel}	1.1	1.0	

Appendix 13

Competitive reactions of the valine derivatives **95** and **96** with NBS.

compound	**95**	**33**	**96**	**73**
^{1}H NMR signal	α-H	α-H	α-H	α-H
t^0	1.714		1.357	
t^1	1.103	0.414	0.862	0.379
$\log(t^0/t^1)$	0.191		0.197	
% reaction	36		36	
% final	64	24	64	28
% accounted for	88		92	
k_{rel} (NBS)	1		1	

compound	**95**	**33**	**96**	**73**
^{1}H NMR signal	α-H	α-H	α-H	α-H
t^0	1.714		1.357	
t^1	1.172	0.379	0.862	0.379
$\log(t^0/t^1)$	0.165		0.197	
% reaction	32		36	
% final	68	22	64	28
% accounted for	90		92	
k_{rel} (NBS)	1		1.2	

compound	**95**	**33**	**96**	**73**
^{1}H NMR signal	α-H	α-H	α-H	α-H
t^0	2.353		2.221	
t^1	1.768	0.337	1.705	0.347
$\log(t^0/t^1)$	0.124		0.115	
% reaction	25		23	
% final	75	14	77	16
% accounted for	89		93	
k_{rel} (NBS)	1.1		1	

Appendix 14

Competitive reactions of the *p*-methylphenylalaninamide **94** and *tert*-butyltoluene (TBT) with NBS.

compound	**94**	**151**	**150a,b**	TBT	α-BrTBT
^{1}H NMR signal	*p*-Me	*p*-CH_2-Br	*p*-Me	*p*-Me	*p*-CH_2
t^0	1.425	(1.041)[a]	(1.202)[a]	1.354	(0.660)
t^1	0.661	0.384	0.223	0.653	0.694
$\log(t^0/t^1)$	0.334	0.136	0.074	0.317	0.312
% reaction	54			52	
% final	46	27	16	48	51
% accounted for	89			99	
k_{rel} (NBS)	2.45	1.0[b]	0.54[b]	2.32	2.29[b]

[a] Rate of product formation.

[b] t^1 value expressed in terms of the corresponding amount of starting material consumed.

compound	**94**	**151**	**150a,b**	TBT	α-BrTBT
^{1}H NMR signal	*p*-Me	*p*-CH_2-Br	*p*-Me	*p*-Me	*p*-CH_2
t^0	1.425	(0.993)[a]	(1.173)[a]	1.354	(0.620)
t^1	0.647	0.432	0.252	0.583	0.734
$\log(t^0/t^1)$	0.343	0.157	0.085	0.366	0.339
% reaction	55			57	
% final	45	30	18	43	54
% accounted for	93			98	
k_{rel} (NBS)	2.18	1.0[b]	0.54[b]	2.33	2.16[b]

[a] Rate of product formation.

[b] t^1 value expressed in terms of the corresponding amount of starting material consumed.

Competitive reactions of the *p*-methylphenylalanine derivative **93** and *tert*-butyltoluene (TBT) with NBS.

compound	**93**	**149**	**148a,b**	TBT	α-BrTBT
^{1}H NMR signal	*p*-Me	*p*-CH2-Br	*p*-Me	*p*-Me	*p*-CH_2
t^0	1.254	(0.828)[a]	(1.202)[a]	1.197	(0.481)
t^1	0.658	0.426	0.052	0.465	0.716
$\log(t^0/t^1)$	0.280	0.180	0.018	0.411	0.396
% reaction	48			61	
% final	52	34	4	39	60
% accounted for		91		99	
k_{rel} (NBS)	1.56	1.0[b]	0.10[b]	2.28	2.20[b]

[a] Rate of product formation.

[b] t^1 value expressed in terms of the corresponding amount of starting material consumed.

compound	**93**	**149**	**148a,b**	TBT	α-BrTBT
^{1}H NMR signal	*p*-Me	*p*-CH_2-Br	*p*-Me	*p*-Me	*p*-CH_2
t^0	1.254	(0.978)[a]	(1.201)[a]	1.197	(0.713)
t^1	0.836	0.276	0.053	0.651	0.484
$\log(t^0/t^1)$	0.176	0.108	0.019	0.265	0.225
% reaction	33			46	
% final	67	22	2	54	40
% accounted for		91		94	
k_{rel} (NBS)	1.63	1.0[b]	0.18[b]	2.45	2.08[b]

[a] Rate of product formation.

[b] t^1 value expressed in terms of the corresponding amount of starting material consumed.